NMRI-97-42

TOXICOLOGY DETACHMENT

THE ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) AND MILITARY RELEVANT INHALATION INJURY: A BRIEF REVIEW

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DECEMBER 1997

INTERIM REPORT FOR THE PERIOD
1 OCTOBER 1996 - 31 DECEMBER 1997

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NAVAL MEDICAL RESEARCH INSTITUTE
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TECHNICAL REVIEW AND APPROVAL
NMRI-97-42

The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

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FOR THE COMMANDING OFFICER

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*

2. REPORT DATE
December 1997

3. REPORT TYPE AND DATES COVERED
1 October 1996 - 31 December 1997

4. TITLE AND SUBTITLE
The Acute Respiratory Distress Syndrome (ARDS) and Militarily Relevant Inhalation Injury: A Brief Review

5. FUNDING NUMBERS
M0096.004.1714

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Naval Medical Research Institute Detachment Toxicology
NMRI/TD
2612 Fifth Street, Building 433
Area B
Wright-Patterson AFB, OH 45433-7094

10. SPONSORING/MONITORING AGENCY REPORT NUMBER
NMRI-97-

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*
A brief overview of fundamental aspects of the continuum of diseases from Acute Lung Injury (ALI) to the more severe form Acute Respiratory Distress Syndrome (ARDS) is given. The review is not technologically comprehensive and is intended as an introductory primer for Naval operational personnel interested in health risks associated primarily with inhalation of smoke. Although there are numerous and varied causes of ARDS from inhalation of combustion products or inhalation injury. In particular, the risk of ALI/ARDS from inhalation of combustion products and smokes. The pulmonary toxicity of some well known smoke constituents is discussed. Inhalation of vesicant chemical warfare agents is addressed as militarily relevant risk factor for ALI/ARDS. A brief synopsis of animal research models of ALI/ARDS is given.

14. SUBJECT TERMS
Acute Lungy Injury, Acute Respiratory Distress Syndrome, Total Lung Capacity, Pulmonary Function Test(s), National Heart and Lung Institute

15. NUMBER OF PAGES
95

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRAC
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

PREFACE

This is one of a series of technical report describing results of the experimental laboratory programs conduced at the Naval Medical Research Institute Detachment (Toxicology). This document serves as a interim report on The Acute Respiratory Distress Syndrome (ARDS) and Military Relevant Inhalation Injury: A Brief Review. The research described in this report began in October 1996 and was completed in December 1997 under Navy Contract No. M0096.004.1714. This study was sponsored by the U.S. Navy under the direction of CAPT Kenneth R. Still, MSC, USN.

The opinions contained herein are those of the authors and are not to be construed as official or reflecting the view of the Department of the Navy or the Naval Services at large.

ABSTRACT

A brief overview of fundamental aspects of the continuum of diseases from Acute Lung Injury (ALI) to the more severe form Acute Respiratory Distress Syndrome (ARDS) is given. The review is not technologically comprehensive and is intended as an introductory primer for Naval operational personnel interested in health risks associated primarily with inhalation of smoke. Although there are numerous and varied causes of ARDS, the focus of this synopsis is on inhalation injury. In particular, the risk of ALI/ARDS from inhalation of combustion products and smokes. The pulmonary toxicity of some well known smoke constituents is discussed. Inhalation of vesicant chemical warfare agents is addressed as militarily relevant risk factor for ALI/ARDS. A brief synopsis of animal research models of ALI/ARDS is given.

ACKNOWLEDGMENTS/DISCLAIMER

This work was performed under the auspices of the Naval Medical Research and Development Command work unit No. 63706N-M00096.004.1714. Opinions contained herein are those of the authors and are not to be construed as official or as representing the view of the Department of the Navy or the Naval Services at large.

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ABBREVIATIONS

Standard chemical and measurement symbols have been excluded excluded

AC	Hydrogen cynanide - blood agent
AECCA	American European Concensus Committee on ARDS
ALI	Acute Lung Injury
AP-1	Transcription protein (factor) -1
ARDS	Acute Respiratory Distress Syndrome
BAL	Bronchoalveolar lavage
CFC	chloro-fluoro-carbon class of organic compounds
CK	Cyannogen chloride - blood agent
CN	Chloracetophenone - tear agent
CS	o-chlorobenzylidene malononitrile - tear agent
CW	Chemical warfare
CX	Phosgene oxime - vesicant
DLco	Diffusing capacity (lung) for carbon monoxide
DM	Diphenylaminochloroarsine - vomiting agent
ECG	Electrocardiogram
ELAM-1	Endothelial Leukocyte Adhesion Molecule -1
ENA-78	Epithelial cell derived Neutrophil Factor - 78
EVLW	Extra Vascular Lung Water - lymph
FED	Fractional Effective Dose
FEF_{25-75}	Forced Expiratory Flow between 25 and 75 % of FVC (mean)
FEV	Forced Expiratory Volume - 1 second
FIO_2	Fractional concentration of inhaled oxygen
FVC	Forced Vital Capacity
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte/Macrophage Colony Stimulating Factor
GSH	Glutathione
H	The terms H, HD, HQ, and HT refer to different formulations of varying purity
HD	and form of sulfur mustard. Bis-(2-chloroethyl) sulfide
HQ	
HT	
HN_1	2,2 - dicolorotriethylamine - nitrogen mustard - vesicant
HN_2	2,2'- dichloro-N-methyldiaethylamine - nitrogen mustard - vesicant
HN_3	2,2',2" - trichloro-triethylamine -nitrogen mustard - vesicant
IL-1	Interleukin 1
IL-8	Interleukin 8
INF- γ	Interferon gamma
LCt_{50}	Lethal Concentration · time product 50%
LD_{50}	Lethal Dose 50%
LPS	Lipopolysaccharide
LTB	Leukotriene B
LTC	Leukotriene C

LTD	Leukotriene D
M-CSF	Monocyte Colony Stimulating Factor
MCP-1	Monocyte Chemotractant Protein 1
MDNAP	Monocyte Derived Neutrophil Activating Peptide
MDNCF	Monocyte Derived Neutrophil Chemotactic Factor
MIP 2	Macrophage Inflammatory Peptide 2
MIP 1	Macrophage Inflammatory Peptide 1
MMAD	Mass Median Aerodynamic Diameter
N-gas	N (number) gas model of combustion atmosphere toxicity
NAD+	Nicotinamide Adenine Dinucleotide (oxidized form)
NATO	North Atlantic Treaty Organization
NFκ- B	Nuclear Factor kappa - B, a transcription factor
NHLI	National Heart and Lung Institute
NOx	Collective term for the oxides of nitrogen
OA	Oleic Acid
OP	Organophosphates - class of nerve agents
PADPRP	poly (adp-ribose) Polymerase
PaO_2	Partial pressure of oxygen (alveolar) - mmHg
pft	pulmonary function test(s)
PGE	Prostaglandins
PGI	Prostacyclins
PS	Chloropicrin - tear agent, incapacitant
SIRS	Systemic Inflammatory Response Syndrome
SM	Collective term for sulfur mustards
TDI	Toluene diisocyanate
TGF	Tumor Growth Factor
TLC	Total Lung Capacity
TNFα	Tumor Necrosis Factor alpha
TxA	Thromboxane A
TxB	Thromboxane B

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INTRODUCTION

In 1967 Ashbaugh and colleagues[1] described a distinctive form of severe, acute respiratory failure in 12 of 272 adult patients requiring respiratory support in two large metropolitan Colorado hospitals. These patients suffered from dyspnea, tachypnea, hypoxemia refractory to oxygen therapy, decreased thoracic compliance, and had radiographic evidence of diffuse pulmonary infiltration. Pathologic examination revealed atelectasis, microvascular congestion and hemorrhage, severe alveolar edema, and hyaline membranes. This clinical, physiologic and pathologic picture was remarkably similar to infantile respiratory distress syndrome. Subsequently this pattern of respiratory abnormalities became known as Adult Respiratory Distress Syndrome (ARDS).[2] ARDS is typified by its rapid onset in patients with no previous history of respiratory disease, and the rapid organization of the acute lesion into pulmonary fibrosis. ARDS is independent of pulmonary congestion due to cardiac insufficiency. Despite application of a variety of empiric approaches to treatment the mortality rate for ARDS remains between 60 to 75%.[3] Mortality estimates for ARDS range as high as 97,500 per year in the US.

BACKGROUND

Many aspects of ARDS have been and are subject to controversy. ARDS has been held synonymous with or known variously by terms such as "wet lung", "shock lung" or "Da Nang lung". This association with various different pulmonary conditions has led to the opinion by some that ARDS may not be a distinctive disease entity.[4,5] Nevertheless, ARDS is widely

recognized and has been the topic of extensive research as well as numerous conferences and a number of books. Despite collection of a great deal of descriptive information regarding the clinical presentation, physiology, pathology, and prognosis of ARDS, there is considerable disagreement as to exactly what ARDS is and what causes it. Whether or not there has been a moderate improvement in the prognosis for ARDS victims over the years and, if so, whether said improvement is a result of treatment(s) is arguable. Perceived improvement in the prognosis may be an artifact of a broadening "definition" of the disease.[6] There is even some question as to whether some treatments have been more detrimental than beneficial. Research has shown that ARDS has a broad based etiology associated with numerous risk factors and a wide variety of causes. Lack of a clear understanding of the role other organ systems play in the pathogenesis and outcomes of ALI/ARDS coupled with a vague definition of the disease has been a source of controversy and a hindrance to the postulation of a well defined pathogenic mechanism.

In 1972 a National Heart and Lung Institute (NHLI) Task Force on Respiratory Diseases[7] estimated 150,000 ARDS cases/year for an incidence of about 75 cases/100,000 population. This figure gained additional credence by popular use in the literature. However, several recent large scale investigations have challenged this figure and have placed the incidence of ARDS at 1/3rd to 1/20th of the NHLI estimate.[8,9] The vague and changing "definition" of ARDS and the emerging concept that the current disease state recognized as ARDS is actually a severe manifestation of a wide continuum of lung injury has contributed to the large discrepancy of estimates of ARDS incidence.[10,11]

In response to the growing controversy and uncertainties surrounding ARDS the American-European Consensus Committee on ARDS (AECCA) was formed, in 1992, under the

auspices of the American Thoracic Society and the European Society of Intensive Care Medicine. The AECCA held a series of conferences in order to bring clarity and uniformity of approach toward many aspects of ARDS. In 1994 the a conference report was co-published simultaneously in the *American Journal of Critical Care and Respiratory Medicine*[12], *Intensive Care Medicine*, and the *Journal of Critical Care.* A return to the original term acute (as opposed to adult) was recommended. This was no mere semantic exercise in that it recognizes that ARDS is not limited to adults. One of the original 12 patients in which ARDS was first described was an 11 yr. old child. There was a consensus of opinion that ARDS be recognized as the severe end of a continuum of the pathogenic process, and the term Acute Lung Injury (ALI) was coined to acknowledge both the spectrum of etiologies and less severe lung disease which is part of the continuum that can lead to ARDS. Simply stated, all patients with ARDS have ALI but not all suffers of ALI have ARDS.

The overall results of the AECCA effort were to make the definition of ALI and ARDS less arbitrary. I doing so, to facilitate more uniform pursuit of research to elucidate the various pathogenic pathways of ALI and ARDS associated with various etiologies. ALI is defined as a syndrome of inflammation and increased pulmonary permeability that is associated with a constellation of clinical, radiological and physiologic abnormalities that cannot be explained by left atrial or pulmonary capillary hypertension. Although the onset of ALI/ARDS may be delayed as much as 4 days after initial insult it progresses in severity very rapidly and this acute phase may persistent for several weeks. ALI/ARDS is associated with known risk factors, and is characterized by arterial hypoxemia resistant to oxygen therapy and the presence of diffuse pulmonary infiltrates. Clinically ALI and ARDS are defined by criteria deriving from four

categories. The distinguishing feature between ALI and ARDS being in severity of oxygenation deficit.

These categories are:

1. Timing. Even though there may be up to a few days between initial insult to the lung and the onset of clinical symptoms ALI/ARDS, when compared to other lung diseases, is acute in onset.

2. Pulmonary hemodynamics. There is no evidence of left atrial hypertension in ALI/ARDS patients (i.e. pulmonary wedge pressure $\leq$ 18 mmHg) suggesting that pulmonary edema is not cardiogenic.

3. Radiography. There is radiological evidence of diffuse bilateral infiltration of the lungs.

4. Oxygenation. Clinically there is a high ratio of arterial partial pressure of oxygen (PaO_2) to fractional concentration of inhaled oxygen (FIO_2). These high ratios often exist even in the presence of high partial pressure O_2 therapy. The severity of the hypoxia as measured by the PaO_2 /FIO_2 ratio is the clinical feature by which ALI and ARDS are distinguished. Those ratios are as follows:

a. ALI - $PaO_2/FIO_2 \leq 300$ mmHg.
b. ARDS - $PaO_2/FIO_2 \leq 200$ mmHg.

It is too early to determine the influence of this "redefinition" of ALI/ARDS has had on estimates of incidence. However, one investigation using these criteria reported essentially no difference in mortality between patients meeting ALI criteria (59%) than those meeting ARDS criteria (57%).[13] Another recent investigation reported an ARDS mortality rate of 62%[14] which differs little from the general "historical" estimate of ARDS mortality.[15]

CAUSES AND RISK FACTORS FOR ALI & ARDS

There are numerous recognized etiologies for ALI (hence ARDS) which fall into two general categories; direct injury to lung tissue and indirect lung injury. Common direct injuries include toxic inhalation, aspiration, near drowning, pneumonia, and lung contusion. Indirect lung injury is thought to be mediated by endotoxin commonly associated with systemic inflammatory response syndrome (SIRS).[16,17] SIRS is itself a complex syndrome surrounded by a similar degree of controversy regarding definitions and other aspects; the details of which are not in the scope of the present discussion. Suffice it to say that SIRS is often held synonymous with sepsis, however, SIRS is not explicitly indicate the presence of infection. Common indirect injuries are SIRS, drug/chemical ingestion, severe non-thoracic trauma, and other organ system diseases such as pancreatitis. SIRS is the primary indirect cause of ALI/ARDS is also is the primary complication of ALI/ARDS. ARDS related death is often due to multiple organ failure, again which can be considered either a cause of or caused by ARDS.

From an toxicology perspective, inhalation injury remains the principal etiology of concern. There are no comprehensive reviews that specifically attribute a percentage of ARDS to inhalation injury. However, estimates ranging from 10 to 35% can be derived from a few studies. There are a few documented incidents of ALI/ARDS related to the inhalation of specific airborne chemicals such as high O_2 ($\uparrow$60%), ZnCl, NH_3, NO_2, Cl_2, phosgene, acrolein, and paraquat. Smoke inhalation, however, is by for the most common and greatest inhalation risk factor. Smoke inhalation is well known as the major cause of death in fire victims. In recent years there have been between estimates ranging from 5,000 to 20,000 per year non-military, non-industrial

fire related fatalities. Eighty percent of which were attributed to inhalation injury.[18] I burn victims advances in treatment have reduced mortality is 2 to 3% in victims without inhalation complication compared to 46% victims with inhalation injury.[19]

Smoke inhalation risk for pulmonary injury is of obvious concern to the general population as well as the military services. Certain military settings present unique non-fire related ALI/ARDS risk factors, such as chemical munitions and atmospheres resulting from detonation of fire arms. One highly specific military ALI/ARDS risk factor is the inhalation of certain CW agents, particularly vesicants. Inhalation injury was listed to be the cause of death in 50% of the fatal vessicant CW agent exposures in WW I. Recent findings from the Iraq-Iran conflict in the 1980's place this figure in the 90th percentile. Although most of the documented cases of CW inhalation injury predate the initial description and recognition of ARDS, the existing medical reports show a pathophysiology considered pathognomonic for ALI/ARDS.[20]

PATHOGENESIS OF ALI/ARDS: Mechanisms and Mediators.

The pathogenesis of ALI/ARDS is extremely complex involving numerous mediators of the inflammatory response and various cellular responses for which the time course, order of events, and interactions are not clearly understood. Extensive research on these cellular and molecular level changes have led to some promising clues as to the pathogenesis of ALI/ARDS.[21,22] However, these investigations also have served to confuse the issue with results that conflict with promising current hypotheses regarding the pathogenic mechanisms. Therefore existing theories of ARDS pathogenesis are constantly evolving. A common statement found in

periodic reviews of ARDS is that less is known of it's pathogenesis than was thought during the previous decade.[23] For example, the overwhelming evidence suggesting that massive influx of neutrophils into the lung was pivotal in the pathogenesis of ALI/ARDS, has been challenged by several well documented reports of the disease in neutropenic patients.[24]

The AECCA found that the pathogenesis of ALI/ARDS could be divided into two broad categories corresponding to etiologic type. Indirect injury can be considered the result of widespread systemic inflammation with or without infection exerting initial effects on pulmonary vascular endothelium. The second category, direct injury, results when there is direct damage to pulmonary parenchyma which leads to initiation of the inflammatory response. Bacterial endotoxin (LPS) can be considered a special case of both categories depending upon where the initial infection is located. The case of pneumonia can be considered much the same as sepsis in that it can be considered both a major cause and a major complication of ALI/ARDS. Regardless, the common focal point for both the direct and indirect categories of ALI/ARDS pathogenesis is the inflammatory pathway. In either category abnormal regulation or modulation of the inflammatory response ("rogue inflammation") at one or more critical points is a fundamental facet in the development of ALI/ARDS.

The inflammatory response can be characterized as having both a cellular and humoral component. Primary cellular components include neutrophils, macrophages, monocytes and lymphocytes. The rate of formation, maturation, movement, and activity of these cells is regulated by numerous mediators, many of which are produced by these same cells. In addition to the elaboration of mediators and regulators of cellular activity, cell products such as selectins and integrins are produced which act on other tissue components. Many of the humoral mediators of

the inflammatory response act to constrict or relax smooth muscle tissues of the vasculature and larger conducting airways. The selectins and integrins mediate the adhesion of neutrophils to vascular endothelial tissue in preparation for transmigration of these cells from the capillaries to the pulmonary epithelial surface. Macrophages and neutrophils release oxidants and proteolytic enzymes which cause additional direct damage to epithelial tissues. Humoral components of the inflammatory response are either constitutive or produced specifically in response to a variety of stimuli. There are those that are relatively independent of the cells upon which they effect such as complement, kinin, and coagulation/fibrinolytic systems; and those that are cell derived such as cytokines, eicosanoids (arachidonate metabolites), neuropeptides, and nitric oxide. Interactions between the cellular and humoral components of the inflammatory response in the pathogenesis of ALI/ARDS are complex. **Figure 1**, although far from complete, illustrates this complexity and contains some of the basic interactions that are part of the inflammatory response in sepsis leading to ALI/ARDS. With exception of a few of the initiating factors the direct injury pathway is similar in many aspects. **Figures 2 and 2a** shows fundamental aspects of the postulated pathogenesis of ALI/ARDS caused by direct injury to the respiratory tract from smoke inhalation. Although much is known of mediated cell to cell and cell to tissue interaction in the inflammatory response, there is a general consensus that much remains unknown that is in need of clarification through systematic investigation. There is yet no convincing hypothesis regarding the existence of a single, typical pathway or sequence of events which underlies all causes of ALI/ARDS. Cochrane[25] states the case well - "No longer is there any illusion that any specific molecule mediates ARDS. Rather it is clear that many of yesterdays putative 'mediators' of ARDS actually are enhancers, amplifiers, modulators and regulators that fine-tune evolution and resolution of the

inflammatory sequences rather than cause them." In addition to injury of endothelial and epithelial tissues many of these mediators elicit physiological responses such as broncho and vaso-constriction (dilation) which are detrimental to lung function and exacerbate tissue damage. A great deal of research has focused on these mediators as potential points of intervention into the pathogenic process and as potential early biomarkers of risk. Many therapeutic approaches have been developed which employ up or down regulation of certain specific actions of these mediators with limited success.

Many of the mediators of ALI/ARDS play multiple roles in the pathogenesis of the disease and several mediators may elicit the same responses in other components of the inflammatory response. A given mediator may either down or up regulate a given action in process depending on the activity of other mediators of the specific sequence of events.

Cellular Mediators[26,27,28,29]

Macrophages and Monocytes

The principal function of macrophages and monocytes is phagocytosis of cellular debris and foreign particles in the lung. However, macrophages and monocytes play several other roles in the pathogenic process. They are prime sources of most of the cytokines and arachidonate metabolites. Macrophages also produce oxidants and release many of the enzymes thought to be responsible for cellular injury. Although the neutrophils are thought to be the primary effector tissue damage be cellular enzymes in ALI/ARDS, macrophages account for much of this damage. This is demonstrated by the fact that ARDS has been found to occur in neutropenic patients. Macrophages function to modulate the degradation and repair processes by taking up excess neutrophil products, cytokines and fibrinogen. In "routine" inflammation and mild ALI there is a

bimodal increase macrophage number and activity. The late stage influx of macrophages and monocytes (following and initial influx of neutrophils) is often associated with resolution of the inflammatory process. In non-survivors of ARDS this latter influx of these cells often is not found.

Neutrophils

At one time neutrophils were considered the singularly most important effector of ALI/ARDS. This was because of marked neutrophil coagulation in the microvasculature and massive influx of neutrophils into the alveolar spaces in almost all ALI/ARDS patients. However, as noted above, evidence of ALI/ARDS in patients with neutropenia demonstrated that neutrophils were not necessarily the sole factor in the advent of the disease. Neutrophils are still considered to be the principal source of tissue damage through release of proteolytic enzymes and toxic reduced species of oxygen (O_2-, H_2O_2, OH) from respiratory burst. Neutrophils produce adhesion molecules (selectins and integrins) which promote adhesion to the vascular endothelium. Endothelial cells also produce adhesion molecules which foster neutrophil attachment to endothelial tissue. These cytokines in conjunction with lysosomal cationic protein increase capillary permeability and thus migration of neutrophils and edema fluid to the alveolar spaces. Neutrophils are a primary target cell for many of the cytokines and eicosanoid mediators which regulate their activity. Thus neutrophils play an important role in both epithelial tissue damage and changes in endothelial permeability. Recent research has shown neutrophils to have an ever increasing role in the production and release of cytokines, although they are not yet considered to be the principal source of these mediators. Neutrophils also have been shown to be cytotoxic to endothelial cells on contact.

Platelets and Fibroblasts

Platelets aggregate together in ALI/ARDS to form microthrombi in the lung, leading to the coagulation in the microvasculature that is seen in this disease. When activated, these cells produce cytokines and eicosanoids (for example thromboxane) which act as mediators of the activity of other cells. Platelet and fibroblast derived cytokines and eicosanoids also elicit potent physiological responses such as broncho and vasoconstriction which can damage alveolar capillary membranes. Fibroblasts along with type II pneumocytes can synthesize and release many of the complement cascade components such as C3 and C5 leading to extensive fibrosis found in the latter stages of the disease.

Humoral Mediators[30,31,32]

Complement, Kinins and Coagulation Factors

Complement cascade factors involved in coagulation stimulate the production of fibrinogen which eventually contributes to the pulmonary fibrosis seen in the latter stages of ARDS. Several of the complement components act as potent chemotractants for neutrophils and monocytes and can stimulate the production and release of cytokines from these cells. Activation of complement alone was once thought to be sufficient to induce ARDS, however it appears that this hypothesis is not incorrect but merely over simplified.[33] Complement activation remains an important part of the pathogenesis scheme but other factors such as macrophage and cytokine mediated events also are critical to the pathogenesis of ALI/ARDS.

Cytokines

Cytokines are small peptide messengers which are synthesized and released by mainly by macrophages but can be produced by number of other cell types as well (**Figure 2**). These

cell-derived peptides cause target cells to alter one or more of their functions which can elicit a direct effect or cause the release of other mediators by these cells. Cytokines are not normally constitutive but are synthesized by the cell on stimulation. Stimulation of cytokine synthesis is itself mediated through a series of mediators such as transcription factors NF-κB, and AP-1.[34] Several substances are known to stimulate the synthesis of cytokines. This includes other cytokines, eicosanoids, immunocomplexes, complement factors, and endotoxin. Although cytokines regulate and moderate the activities of other effector cells they also act to produce direct effects such as broncho- and vasoconstriction. Cytokines implicated in the pathogenesis of ALI/ARDS are listed below with their common abbreviations. In many cases specific actions can be attributed to specific cytokines, however, it is not certain that all effects of a specific cytokine are known. The specific actions of these and other cytokines is an interesting study, but is beyond the intended scope of this review. Typical cytokines thought to be involved in the pathogenesis of ALI/ARDS are:

Tumor necrosis factor (TNFα).

Endothelin.

Epithelial cell derived neutrophil factor (ENA-78).

Interleukins, 1 & 8 (IL-1,IL-8).

Macrophage inflammatory peptides (MIP-1, MIP-2).

Monocyte derived neutrophil chemotactic factor (MDNCF).

Monocyte derived neutrophil activating peptide (MDNAP).

Transforming growth factors (TGFs).

Interferons (INF-γ).

Colony stimulating factors ((M-CSF (monocyte), GM-CSF (granulocyte Macrophage), G-CSF (granulocyte)).

Monocyte chemotractant factor (MCP-1).

Endothelial Leukocyte Adhesion Molecule (ELAM -1).

Typical actions elicited by cytokines thought to be involved in ALI/ARDS pathogenesis are:

Stimulation of other cells for cytokine release.

Monocyte, neutrophil, and platelet chemotaxis and activation.

Cytotoxicity (endothelial and epithelial).

Mediate bioactivity (vasoactivity and bronchoactivity).

Inhibit surfactant function.

Elevate production of histocompatibility antigen.

Precipitate angiogenesis.

Stimulate arachidonate metabolism (production of eicosanoids).

Stimulate monocyte formation in bone marrow.

Stimulate adhesion of leukocytes to vascular endothelium.

Eicosanoids

Eicosanoids are products of arachidonate metabolism and therefore are products of membrane lipid phospholipid metabolism. They fall primarily into three categories depending on the specific metabolic pathway. Prostaglandins ((PGEs - which includes thromboxanes (TxA, TxB), and prostacyclins (PGIs)) are produced by the cyclooxygenase pathway. Leukotrienes (LTs) and epoxides are derived from the lipoxygenase and monoxygenase metabolic pathways respectively. Of these the prostaglandins and leukotrienes are thought to be the most important in

the ALI/ARDS pathogenesis. Generally PGEs and PGIs are decreased and TxA, TxB and leukotrienes (LTB, LTC, LTD) are elevated in ALI/ARDS. The eicosanoids elicit responses on cells and tissues in a manner similar to the actions of many of the cytokines. Thus they also mediate many of the events in the inflammatory response. However, recent evidence suggests that the principle role of the eicosanoids is modulation of the inflammatory process primarily through simulation of cytokine synthesis. The actions of the PGEs and PGIs inhibit the actions of the Txs and LTs and are thought to be beneficial by limiting many of the events which lead to ALI/ARDS. PGEs have been used as treatment for the disease. Whereas harmful eicosanoid effects, usually mediated by the Txs and LTs, include increasing endothelial and epithelial permeability and chemotaxsis and activation of neutrophils and macrophages. The eicosanoids also elicit potent tissue level responses such as vasoconstriction and bronchoconstriction which indirectly damage tissue and potentiate the pathophysiologic effects of ALI/ARDS.

Other Mediators

Other mediators such as the transcription factors previously mentioned, endogenous NO, growth factors, and many of the pulmonary neuropeptides such as substance P also play important roles in the pathogenesis of ALI/ARDS. For example G-CSF has been shown to stimulate maturation of stem cells to neutrophils, stimulate neutrophil adhesion of endothelium, prolong neutrophil life, and activate neutrophils. However, the exact roles and degree of importance to the pathogenesis of ALI/ARDS of many of these other possible mediators is not yet clearly understood. In many cases all is known is that at various stages in the disease process there is either an excess or a depletion of these mediators.

As noted earlier, at present it is doubtful that a single series of events can be identified as THE path to the development of ALI/ARDS, particularly since the disease has a wide variety of etiologies each of which may have a unique pathogenesis.

Surfactant[35]

The surfactant system is crucial for maintaining patency of the alveolar spaces. Only recently has the disruption of the surfactant system been fully appreciated in the pathophysiology of ALI/ARDS. A variety of surfactant abnormalities occur in injured lungs. Damage to type II pneumocytes causes a depletion of the surfactant pool and abnormalities of surfactant metabolism. Abnormalities of surfactant composition and inactivation of surfactant proteins leads to atelectasis and collapse of alveoli. Some inhaled toxins may effect surfactant directly and influx of serum protein in edema fluid into the alveolar airspace causes both a dilution and inactivation of surfactant. However, as with most aspects of ALI/ARDS, the mechanisms and timing of surfactant dysfunction in the pathogenetic process is not well understood. Promising effects have been observed in some studies utilizing treatment of ALI/ARDS patients with exogenous surfactant. Animal models of ALI/ARDS have responded well to surfactant replacement treatment. Despite some encouraging results, other studies have not demonstrated that surfactant replacement is an effective treatment for ALI/ARDS. Thus the efficacy of surfactant replacement treatment remains equivocal. Problems may exist with timing, dose, optimal composition and specific delivery of exogenous surfactant in treatment strategies.

PATHOLOGY OF ALI/ARDS

Increased pulmonary microvascular permeability followed by alveolar edema rich in serum proteins has long been denoted as a hallmark of ALI/ARDS.[36,37,38] The AECCA emphasized that both endothelial and epithelial injury are critical for ALI/ARDS and that these should be defined pathophysiologically in quantitative terms whenever possible. In smoke inhalation victims, ALI/ARDS typically develops from 6 to 72 hr post exposure. Mortality may occur within a 3 to 6 days of onset with rare cases extending to months. Thus there appears to be a delay in onset of ALI/ARDS from a "dose"/response perspective. Clinically the onset and progression ALI/ARDS is acute and rapid.

The pathology of ALI/ARDS has been subdivided into three overlapping phases as follows:

1. Exudative - acute, edema and hemorrhage.
2. Proliferative - subacute, organization and repair.
3. Fibrotic - acute, end-stage fibrosis.

The exudative phase is characterized by diffuse alveolar damage with necrosis of type I pneumocytes. There is evidence of endothelial swelling with a widening of the gap junctions between the cells. Widening of the alveolar septa allows infiltration of protein rich edema fluid to the alveolar space. Extensive influx of neutrophils is a hallmark of ALI/ARDS. Neutrophils may account for 85% of the cellular component of bronchoalveolar lavage (BAL) fluids compared to a normal less than 5% level. Studies suggest that there is up to a 10 fold increase in the production and maturation of stem cells into neutrophils. Eosinophilic hyaline membranes in the

terminal airways are common. There is a marked increase in BAL fluid oxidant activity during this phase.

The proliferative phase is best characterized as the period of time when the alveolar infiltrates organize into so called granulation tissue. There is a proliferation of alveolar type II pneumocytes and fibroblasts with high levels fibronectin and hyluronic acid in the extravascular lung water heralding the onset of fibrosing alveolitis. Marked interstitial fibrosis is present, with thickened alveolar walls collapsing on one another (indurition). Bronchiolitis obliterans or filling of terminal and respiratory airways with organizing fibrous exudate is uncommon in ARDS but alveolar ducts often are obstructed with fibrinous fluid. Fibronectin coating of the fibrinous exudate is more prominent in the proliferative phase than in the exudative phase.

The chronic fibrotic phase is characterized by remodeling of the parenchyma and microvasculature. Collagen and collagenous tissue containing very few cells fill alveolar spaces and thickened alveolar septa have a high connective tissue content. Remodeling of the parenchyma can proceed to formation of large granulomatous cysts. Microvascular endothelial tissue is replaced by collagenous tissue. Extensive replacement of normal epithelial and endothelial tissue with collagenous connective tissue can result in distorted lung architecture as seen in bronchopulmonary dysplasia. Recently, markers of collagen metabolism were shown to be significantly more elevated in BAL fluid and sera of ALI/ARDS patients than in patients with pneumonia. Elevated collagen precursors were found in patients with or without subsequent histologic evidence of intraalveolar fibrosis. These markers could be attributed to collagen synthesis as opposed to collagen degradation.[39]

LONG TERM SEQUELAE OF ALI/ARDS

Nearly all survivors of ALI/ARDS have some degree of permanent respiratory dysfunction in the form of at least mild hypoxemia with exercise[40,41,42,43,44]. Yet, remarkably, 40 to 50% of the survivors of even severe ARDS recover and do not exhibit clinically significant respiratory dysfunction. The majority of the 40 to 60% of ALI/ARDS survivors with long-term pulmonary dysfunction are either less than 20 or greater that 50 years of age. Oddly, there seems to be no correlation between of indices of acute ARDS severity and the presence of significant long term sequelae. Recovery usually occurs with in 3 to 6 months after the acute phase ends. Beyond 6 months there is little improvement if dysfunction is still present at this time. Follow up pulmonary function tests (pfts) have been conducted on ALI/ARDS survivors periodically for one to two years with some reported cases extending to 7 years. By standards recommended by the American Thoracic Society clinically significant pulmonary dysfunction is typically restrictive and is normally manifested in more than one function test. The most common dysfunction is reduced gas exchange as measured by transfer factor or diffusing capacity for carbon monoxide (DLco). Significantly reduced DLco is found in 78% of those who suffer permanent dysfunction. Restricted expiratory flow indicating possible loss of elastic recoil and/or airways restriction is found in 54% of those with respiratory dysfunction. This is shown by reduced values of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), the ratio of these (FEV_1/FVC), and forced expiratory flow between 25 and 75% of FVC (FEF_{25-75}). Total lung capacity (TLC) is reduced in 41% of those with significant dysfunction. Dysfunction can be determined by the measurement of other pfts that are not routinely performed such as quasistatic and dynamic compliance. In 45% of those who suffer pulmonary dysfunction the disability is

severe enough that they are not able to return to the work in which they were previously engaged. In approximately 25% the severity of the dysfunction prohibits return any type of gainful employ. Marked airway hypersensitivity is present in about 30% of ARDS survivors.[45]

SMOKE INHALATION INJURY

Thermal Injury

There are three types of smoke inhalation injury, thermal injury, anoxic injury, and chemical injury[46,47] Smoke temperatures of 260 to 280 °C are common in fires and direct thermal injury occurs when this heat energy is transferred to lung tissues. Thermal injury also can be caused by deposition of hot aerosol particles in the respiratory tract. Heat energy can be released from further oxidation of incompletely combusted fire gases in the airways. Thermal injury is thought to be largely confined to the upper airways. The upper airways are efficient heat exchangers designed to humidify and warm inspired air. These same features act to protect the lower respiratory tract from thermal injury. Heat damage to lower airways and lung parenchyma is uncommon, with estimates of thermal burns beyond the larynx from 0.1 to 5 %. For example, Pruitt[48] found convincing evidence of thermal injury to lower airways in only one of 697 patients. It is not likely that thermal injury plays a direct role in initial parenchymal damage seen in smoke related ALI/ARDS. Dressler[49] noted "...heat is not a factor in the lower airway in the sense that one cannot actually burn the alveoli without incinerating the victim". However, this does not mean that the role of thermal injury in ALI/ARDS pathogenesis can be completely discounted

because the contributions of hot particulate deposition and *in situ* combustion of incompletely oxidized gases is not well understood.

Anoxic Injury

Combustion gases are produced in high enough concentrations to cause sufficient displacement of atmospheric oxygen to induce anoxic injury. Transient reduction of O_2 to as low as 2 % has been reported in combustion atmospheres in closed spaces. Oxygen concentrations 5% or less in closed environments are not uncommon[50]. Anoxic injury can be associated with even transient exposures to O_2 concentrations commonly found in combustion atmospheres. Hypoxic atmospheres also can potentiate the toxic effects of other constituents in combustion atmospheres.

Chemical Injury

Thermal and anoxic injury may contribute to pulmonary injury associated with inhalation of smoke, but the primary causes are the toxic chemical constituents of smoke. Crapo[46] defines smoke as the generic term describing the gases and suspended particulates associated with fires. The composition of a given smoke is determined not only by the composition of the burning material but by temperature, rate of temperature rise, duration of burn, oxygen content, and humidity as well. The chemical constituency of smoke is highly varied and complex with constituent counts numbering in the thousands. Consequently, smoke toxicity is highly varied. There are several well known toxins that are routinely found in smokes from several sources, many of which contribute to inhalation injury either directly or indirectly.

Aerosol Particles

Aerosol particles (solid and low vapor pressure droplets) are one of the fundamental constituents of smoke. The chemical constituency of aerosol particles in smoke is as varied as the chemical constituency of the smoke in general. For instance, as many as 2500 compounds have been identified in the particulate phase of tobacco smoke. Thus addressing the toxicity of smoke particles is not straight forward. Even though carbon black is one of the principal constituents of smoke aerosols and is often regarded as chemically inert, there is still pulmonary toxicity that can be attributed to the particles themselves. Smoke aerosol concentrations between 1 and 15 g/m^3 have been reported[51,52] with the typical concentration being 4.5 g/m^3. The particle size distributions are often bimodal, with the mass median aerodynamic diameters (MMAD) of the modes ranging from 0.2 - 1.8 μm and 3 to 5 μm. Despite wide particle size distributions (geometric standard deviations up to 4), practically all smoke aerosol particles are respirable with a significant fraction capable of penetrating deep into the respiratory tree.

While direct irritation and thermal damage of lung parenchyma by particles is possible the primary toxic effects of particles are those exerted on macrophages and other phagocytic cells in the lung. Breathing a 1 to 2 g/m^3 aerosol with an MMAD of 1 μm for one hour would result in sufficient pulmonary (alveolar) region deposition of particles to induce the dust overload phenomenon[53]. Dust overload occurs when normal pulmonary alveolar macrophage function is compromised causing the release of oxidants and enzymes from these as well as other phagocytic cells which in turn causes direct damage to other lung tissue. Particles are capable of stimulating the release of cytokines and are chemotractants for neutrophils thereby setting off the cascade of events in the inflammatory response which can lead to ALI/ARDS[54]. Toxins which normally

would not penetrate to lung parenchyma can be carried on particles reaching these tissues resulting in lung damage.

CO and CO_2

Carbon dioxide and carbon monoxide are formed by the combustion and incomplete combustion of organic materials respectively. CO_2 is relatively innocuous but exerts two important effects which promote toxicity. It it is a primary factor in displacement of O_2 and anoxic injury. CO_2 also is a potent stimulator of breathing causing increased delivery of other combustion toxins. Although many other toxins have been identified in smoke CO is still the most dangerous. The primary effect of CO poisoning is its high affinity binding to hemoglobin and subsequent reduction of both blood O_2 carrying capacity and the ability of hemoglobin to release O_2. This reduction of O_2 delivery may increase tissue injury. CO also binds to cytochrome oxidase inhibiting oxidative metabolism at the cellular level, which may account for some tissue damage in the lung[55]. Other toxic effects of CO on the lung include impairment of mucocillary clearance, increased bronchial gland secretions, and interference with type II pneumocyte oxidative reduction reactions. CO also has been reported as an important factor in the pathogenesis of permeability edema[56], which is consistent with findings in our laboratory[57].

CO concentrations as high as 57% in combustion atmospheres have been reported[58] however typical CO concentrations range from 0.1 to 10 %[59]. According to the Coburn-Foster-Kane relationship, breathing 1% CO for a few minutes would cause lethal 70 to 80% carboxyhemoglobin levels. Exposure response relationships for clinically significant lung damage from CO exposure are not known.

HCN

Like CO, cyanide is an asphyxiant commonly found in smoke. Cyanide is produced from incomplete combustion of nitrogen containing materials such as wool and many of the synthetic fabrics and building materials. Peak smoke HCN concentrations in confined enclosed spaces typically range from 200 to 400 ppm with values as high as 1,720 being reported[60,61,62,63]. Exposure to 280 ppm HCN causes immediate death[50]. Cyanide blocks oxidative metabolism by binding to cytchrome a-a_3. Oxygen transport is uncoupled preventing mitochondria from utilizing O_2 and cytotoxicity can result[64,65]. Cellular metabolism is shifted to anaerobic pathways with a resulting production of lactate. Metabolic acidosis from tissue lactate build up stimulates breathing thereby increasing the exposure to other toxins in smoke.

Irritant Gases

There are numerous irritant gases and vapors found in smoke, many of which are directly cytotoxic by a number of mechanisms. Highly water soluble gases and vapors will be deposited primarily in the upper respiratory tract where as gases with lower water solubility will penetrate deeper into the respiratory tree[66].

1. Acid gases - HCl and HF.

Hydrochloric acid (HCl) is a constituent of smokes from burning plastics (primarily PVC) and is found in concentrations ranging from 450 to 15000 ppm[67,68]. The upper airways are the focal point for inhalation injury from these highly water soluble acid gases. Exposure to 5 to 10 ppm causes irritation of the mucous membranes of the eye and throat. Concentrations of 1,000 to 2,000 ppm are thought to be fatal in 10 minutes. HCl pulmonary toxicity is thought to include acute bronchitis, laryngeospasm, glottal edema and pulmonary edema. Whether or not HCl

adsorbed on to aerosol particles promotes the development of pulmonary edema is controversial and subject to additional research[50,69,70].

Hydrogen fluoride (HF) can be released by heating and combustion of coal, and from natural materials made of clay such as brick, tile and minerals such as cryolite[71]. However, a greater potential threat is the release of HF in very high concentrations on combustion of its CFC (chloro-fluoro-carbon) fire suppressants. Certain CFC replacements for the Halon fire suppressants can produce concentrations of HF as high as 50,000 ppm when deployed and release of 1400 to 5000 ppm is typical[72]. Like HCl, HF is highly water soluble and forms hydrofluoric acid which is normally adsorbed in the upper airways, where it is irritating and can cause necrosis of mucous membranes. Hydrofluoric acid in aerosol droplet form can penetrate to deep lung, which is of particular concern when CFC suppressants are used with water mist systems to suppress reflash of fires. Acute inhalation of 120 ppm of HF for 1 min. produced marked respiratory irritation in volunteers, and hemorrhagic pulmonary edema has been reported in individuals who received concurrent brief inhalation exposure from being splashed in the face with HF[73]. The one hour LC_{50} in rats for HF exposure is approximately 1,200 ppm.

2. Chlorine

Chlorine (Cl) is a powerful oxidizing agent with several common industrial uses and is found in some combustion atmospheres. Chlorine is thought to be 20 times as toxic as HCl[64]. It forms hypochlorous (HOCl) and HCl with the release of free radicals. Chlorine concentrations of 3 to 6 ppm are irritating to mucous membranes, while concentrations of 40 to 50 ppm can cause bronchospasm and delayed onset pulmonary edema. 1000 ppm is rapidly fatal.

3. Ammonia

Ammonia (NH_3) is produced by combustion of wool, silk, nylon, melamine resins and plastics. When NH_3 comes in contact with water in the respiratory tract ammonium hydroxide (NH_4OH) is formed. NH_4OH is a strong alkali which dissociates to form hydroxyl ions leading to the sloughing of the mucosa and liquefaction necrosis. Ammonia is thought to have a high affinity for particulates and therefore can penetrate into the deep lung. Penetration to the lower airways causes severe bronchoconstriction and pulmonary edema[64,66]. Acute exposure to high concentrations causes rapid formation of laryngeal edema with subsequent asphyxiation, Reported injuries from inhalation of NH_3 include airway obstruction, tracheitis, bronchiectasis and ARDS. Severe symptoms may be delayed over 6 hours after exposure. The olfactory threshold of NH_3 is 5 ppm and 20 ppm can be irritating. Incapacitation from blinding may result in inability to escape leading to fatal inhalation injury. It is estimated that inhalation of 1000 ppm for 10 min. is lethal. Smoke concentrations of NH_3 may reach 100 to 200 ppm.

5. Sulfur Dioxide

Sulfur dioxide (SO_2) is a primary by product of the combustion of sulfur containing materials. It is rapidly hydrated on contact with mucosal surfaces to form sulfurous acid (H_2SO_3) and sulfuric (H_2SO_4) acids. These acids are extremely irritating and cause coagulation necrosis of the upper airways. Concentrations below 50 ppm are deposited in the naso- and hypopharynx and 6 to 10 ppm causes irritation to nasopharyngeal tissues[46,65]. At higher concentrations droplet aerosols of these acids are formed in the moist air of the respiratory tract and are capable of penetrating to the lower airways. Deposition of these droplets in the lower airways and on pulmonary parenchyma result in direct injury and edema. SO_2 also causes broncho- and

vasoconstriction which leads to changes in pulmonary oncotic and hydrostatic pressure. This pressure imbalance promotes fluid movement to the alveolar spaces, adding to the severity of pulmonary edema caused by direct tissue damage. A 500 ppm exposure for 10 minutes is estimated to be lethal[66].

5. Nitrogen Oxides - NOx

The oxides of nitrogen (NOx) include nitrous oxide (N_2O), nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen trioxide (N_2O_3), nitrogen tetroxide (N_2O_4), and nitrogen pentoxide (N_2O_5). NO and NO_2 are the two most important toxicologically. Combustion of organic nitrogen containing materials such as cellulose nitrate at high temperatures produce NO which oxidizes to NO_2, which on a mole per mole basis is far more toxic than NO[74]. However this reaction is reversible thus the net oxidation of NO to NO_2 occurs slowly. Because of this ongoing equilibrium the generic term NOx is used to describe exposure this mixture of nitrogen oxides. Nitrogen dioxide is a strong oxidizing agent and unsaturated lipid components of biological membrane are primary targets for oxidation by NO_2. Although it is relatively insoluble, NO_2 can react with water to form nitrous acid (HNO_2) and nitric acid (HNO_3). These acids reach maximum concentration in the distal conducting airways, and terminal and respiratory bronchioles; thus the most severe tissue damage from NO_2 exposure is found in these smaller airways and alveolar ducts. Extensive cell death leads to hemorrhagic pulmonary edema. Because of its relative insolubility there is little or no upper respiratory irritation to serve as an exposure warning. Symptoms of acute lung injury and edema may be delayed by as much as 72 hours after exposure, thus the initial injury may pass unnoticed and still result in death several days later. Despite almost universal citation as a common constituent of smoke there is a paucity

of data regarding NOx concentration in smoke. A few studies have reported smoke concentrations of NOx ranging from 3 to 250 ppm[75]. In munitions testing atmospheres NOx concentrations of 90 to 170 ppm have been reported. Exposure to concentrations as little as 5 ppm have been associated with long term changes in pulmonary function. Exposure to 50 ppm for 1 hour can cause increased epithelial permeability and edema. Exposure to 200 ppm for a few minutes can lead to severe pulmonary damage[66]. NO_2 exposure also causes methemoglobin formation, however the toxicological significance of this to smoke induced acute lung injury is not clear.

6. Hydrogen Sulfide

Hydrogen sulfide (H_2S) is an irritant gas with the odor of rotten eggs capable of inducing inflammation of the mucosa. It is present in high concentrations in petroleum and natural gas deposits. H_2S is a common product of the combustion of high-sulfur fossil fuels; both oil and coal. Concentrations up to 10 to 12 % are found in some oil fields near well head burn-off sites. Concentrations between 2,000 and 4,000 ppm have been reported from the combustion of organic materials for the production of fertilizer. Acute exposures to 1,000 ppm cause immediate respiratory failure and death from acute bronchospasm and mucous hypersecretion[76]. Brief exposures to 100 ppm commonly causes irritation to mucous membranes. There are reports of bronchial irritation resulting from a few hours exposure to concentrations estimated to be less than 1 ppm[77]. Exposure to 800 ppm for less than 2 minutes causes cessation of mucocillary activity. At high concentrations (several hundred ppm or more for 15 minutes) H_2S causes respiratory difficulty, delayed onset hemmorrhagic pulmonary edema and cardiovascular abnormalities[78,79,80]. Permanent neurological damage shown by abnormal ECG and characterized

by memory impairment and amnesia may also result from these exposures. The critical toxic effect of H_2S is thought to be cellular hypoxia caused by inhibition of cytochrome oxidase[81]. Slow dissociation of the H_2S-cytochrome complex is responsible for the persistence of the neurological effects and may be responsible for the delayed onset of many of the pulmonary effects.

Free Radicals

The discovery of the formation of stable free radicals in combustion atmospheres has recently stirred interest in the potential biological effects of these smoke constituents. Free radicals have been found in concentrations up to 1,200 ppm in fire environments[82]. Unidentified, stable free radicals have been shown to cause peroxidation of pulmonary surfactant leading to loss of surface tension and atelectasis. This pulmonary collapse was sufficient to induce hypoxia and unconsciousness. Free radicals are thought to have a role in direct injury of type I and II pneumocytes through membrane lipid peroxidation. Free radicals also are thought to stimulate synthesis of cytokines and inhibit normal function of pulmonary macrophages leading to the early inflammatory responses found in ALI/ARDS. The role of propagation of endogenous free radicals by those in smoke in lung injury is not well understood.

Organic Vapors

Incomplete combustion of organic fuels results in the production of a multitude of organic vapors and aerosols. For example, over 5,000 compounds have been identified in the vapor and particulate phases of cigarette smoke. The exact constituency of any given combustion atmosphere is practically impossible to determine. However several well known organic vapors have been found to be ubiquitous in combustion atmospheres at concentrations of toxicological concern.

1. Carbonyls - Phosgene

Phosgene (Carbonyl Chloride, $COCl_2$) is a potent pulmonary irritant which has been used as a chemical weapon and is produced by the combustion or pyrolysis of chlorinated hydrocarbons, most commonly polyvinyl chloride. Phosgene is considerably more toxic than Chlorine. $COCl_2$ concentrations up to 1,430 ppm have been found in atmospheres produced by combustion or thermal decomposition of chlorine containing compounds[83]. However, at very high temperatures $COCl_2$ itself decomposes. Therefore $COCl_2$ concentrations ranging from 0.2 to 15 ppm are more commonly found in combustion atmospheres[84]. There are numerous reports of the delayed (hours to days) development severe lung injury and death in humans following accidental, short term exposures to $COCl_2$ Inevitably there is clinical indication of diffuse pulmonary infiltration and poor ventilation. Due to relatively low water solubility the primary site of damage is the small airways and the alveoli, where phosgene causes necrosis of the epithelium. Endothelial damage also is present, resulting in atelectasis, alveolar flooding, and eventual granulation of the infiltrate. Bronchial plugging with cellular hyaline membrane and cellular debris has been observed. In at least one reported case the exposure was fairly well documented at 15 ppm exposure for approximately 3 hours. Several studies in large animals have demonstrated similar results with severe pulmonary injury resulting from 30 min. exposures to concentrations ranging from 5 to 87 ppm. Significant decrease pulmonary gas exchange capacity which persisted for up to 8 hours post exposure has been demonstrated after 30 min. exposures to concentrations as low as 0.5 ppm[85]. Survivors of acute phosgene exposure exhibit the long term sequelae of ALI/ARDS.

The fundamental mechanism of action of phosgene lung toxicity has not been firmly established. Some evidence suggests that phosgene slowly hydrolyzes in the lung to HCl and CO_2, thus HCl is thought to be the ultimate toxin[66]. However, a number of experiments have shown that binding of the carbonyl group to free amines of cellular proteins may be the cause of phosgene induced cytotoxicity[86]. Ivanhoe and Meyers[87] showed that the acute pulmonary edema may be neurogenic, caused by release of pulmonary vasoactive peptides. This line of reasoning has been corroborated recently by Bauer and colleagues[88].

There is empirical evidence leading to the conclusion that fatal phosgene poisoning of a worker was caused by inhalation of a low concentration of phosgene coupled with inhalation of particulate matter[89]. However, augmentation of phosgene toxicity by adsorption and delivery on aerosol particles has yet to be verified experimentally.

2. Isocyantes - Toluene Diisocyanate

Toluene diisocyanate ($CH_3C_6H_3(NCO)_2$, TDI) is a precursor in the manufacture of polyurethane plastics[90,91]. It is a primary product of thermal decomposition and combustion of plastics and materials using polyurethane based binders[92,93]. Pyrolysis of flexible urethane foams has been shown to produce atmospheric concentrations of TDI of 2300, 6300, 2800, and 4100 at temperatures of 300, 500, 700 and 1,000 °C respectively[94].

There are two toxicological concerns with TDI; a primary irritation and injury of mucosal (particularly respiratory tract) tissues to which all persons are susceptible to some degree and a hypersensitivity or allergic response at lower levels of exposure which produce the primary response in individuals sensitized by previous exposure[95]. In non-sensitive individuals the primary irritancy response of the respiratory tree is elicited by acute exposure to concentrations as low as

0.03 to 0.07 ppm[95,96]. In most cases the acute irritancy response is reversible[96]. Short term exposure to higher concentrations (0.15 ppm) can lead to tracheitis, asthmatic bronchitis[97], bronchoconstriction, and finally bronchospasm which can be fatal. Severe respiratory symptoms including hemoptysis were reported[98] as early as 30 minutes after initial exposure to 0.10 to 0.12 ppm TDI. The four hour LC_{50} in small laboratory rodents reported by Duncan and colleagues[99] ranged from 9.7 to 13.9 ppm. Hemorrhagic pulmonary edema was found in the animals that died whereas survivors had emphysematous lesions.

Cases of sensitization to TDI developing within one year has been shown batch molding plant workers where daily TDI concentrations ranged from 3 to 12.3 ppb[100]. Sensitization to TDI has been shown in 20% of workers exposed on a regular basis. Guinea pigs and monkeys exposed repeatedly (3 times) to concentrations of 0.2 to 5 ppm for 6 hour periods have demonstrated an immediate airways hyperreactivity response on re-exposure to concentrations of TDI as low as 0.02 ppm. A hyperreactivity response was not demonstrated upon re-exposure of animals initially exposed to lower concentrations of TDI. Thus appears that there is a sensitization threshold concentration occurring between 0.5 and 5.0 ppm for TDI under these conditions[101].

TDI reacts rapidly and exothermically with water producing an unstable carbamic acid which dissociates to form a primary amine and release CO_2[102]. TDI also reacts vigorously with organic molecules containing reactive hydrogen atoms, especially those bonded to oxygen, nitrogen, or sulfur[95]. Therefore, TDI reacts readily with proteins which are rich in -OH, -NH, and -SH moieties. These reactions cause abnormal cross links in enzyme proteins. Abnormal structure and function of critical enzymes eventually leads to cell death. Both the exothermic

hydrolysis and the protein cross linking reactions are mechanisms of TDI primary pulmonary toxicity. TDI also can react additively with proteins forming TDI-protein conjugates which act as antigens causing hypersensitization. Very high levels of exposure to TDI have been shown to produce gastrointestinal effects, however TDI toxicity is "overwhelmingly" pulmonary[103].

3. Styrenes

Styrene ($C_6H_5CH{=}CH_2$) is used in the manufacture of a variety of products such as synthetic rubber and, when polymerized, is most commonly used to make containers, particularly for the food industry[104,105]. Styrene has been found to compose 0.76 to 2.3 % by mass of the volatile products from combustion of gasoline[106]. Styrene monomer constitutes the main volatile product of polystyrene pyrolysis, with concentrations ranging from 0.6 to 100 % of the mass of material volatilized depending on pyrolysis conditions. The amount of styrene monomer produced is a function temperature. Styrene composes from 40 to 60 % of the volatiles evolved from thermal decomposition of polystyrene and 60 to 100 % of the volatiles from flash pyrolyzed polystyrene[107]. Consequently styrene concentrations in combustion atmospheres can be very high. Concentrations as high as 128 mg/L (≅30,000 ppm) styrene have been reported in tests which simulated the burning of a polystyrene insulated television cabinets in a 100 cubic foot room[108].

The central nervous and respiratory systems are the primary target organs for styrene toxicity. No deaths of humans exposed to styrene have been reported[104,105]. Exposure to 216 ppm styrene monomer for 20 min. caused upper respiratory irritation in human volunteers[109]. Symptoms typical of central nervous system depression appear to be the most sensitive end point for styrene exposure by the inhalation route. Exposures in the 50 to 200 ppm range have resulted in a number of symptoms including impairment of balance, altered reaction times, sensory

neuropathy, and concentration decrement[110]. Exposure to 800 ppm styrene has been shown to produce neurological symptoms within minutes of exposure[111]. In rats the 2 hr. LC_{50} for styrene is 2,770 ppm. Acute exposure of guinea pigs to 1300 ppm styrene has been shown to produce pulmonary edema with multifocal hemorrhage and leukocytic infiltration[112]. The toxicokinetics of styrene in man and animals is relatively well known and it appears that the acute toxicity of styrene is unrelated to its biotransformation. However styrene is highly lipophilic and the neurological effects of styrene have been attributed to disruption of cell membrane function. Styrene pulmonary cytotoxicity also has been cited as the result of binding to cell membrane lipids. Styrene oxide, a reactive epoxide intermediate of styrene metabolism has been cited as the ultimate toxin in styrene toxicity[113]. However, as noted above, this others have not observed a correlation between styrene toxicity and styrene metabolism.

4. Aldehydes - Acrolein

Acrolein (CH_2=CHCHO) is a common aldehyde found in pyrolysis and combustion atmospheres. Produced by incomplete combustion of organic materials, it has been identified in the combustion atmospheres of numerous plastics and is prevalent in wood fires[114,115,116,117]. Burgess[118] found acrolein in over 90% of 120 building fires. Acrolein concentrations up to 190 ppm in combustion atmospheres have been reported.

Acrolein is a potent pulmonary toxin, eliciting a variety of responses in the respiratory tract. It has been used as a chemical munition because it is severely irritating to eyes and upper respiratory mucosa at low concentrations[119]. Exposure to 0.5 to 1.0 ppm has been reported to cause immediate irritation of optical and nasal mucosa in humans[120]. Severe respiratory problems have been reported in a victims of accidental acrolein exposure in an industrial settings

where it is a common byproduct of plastic manufacture. Severe pulmonary complications were reported in a worker accidentally exposed to an unknown concentration of acrolein vapor after being splashed in the face. Twenty hr. post exposure the victim was hospitalized with frothy exudate, cyanosis and acute respiratory failure. After two months the right bronchus was occluded and the upper trachea showed signs of hemorragic edema. At 18 months the victim had developed chronic bronchitis and emphysema[121]. Momentary (approximately 5 seconds) exposure of one of the authors (E. Kimmel) to 600 ppm in a laboratory accident, caused dyspnea, nasopharyngeal irritation, and radiological evidence of moderate pulmonary edema within 24 hours of exposure. These symptoms persisted for several days.

Acute exposure of animals to acrolein has been shown to elicit a variety of respiratory and pulmonary effects. Exposure to low concentrations of acrolein produces respiratory depression in a variety of species[118]. The dose-response relationship for lethal acrolein exposure is very steep. One investigation has reported a four hour LC_{50} in rats for acrolein of 8 ppm[122], whereas in a similar investigation, now mortality was produced by two hr. exposure of rats to 2.5 ppm acrolein. In this same study 60% mortality was observed after two hr. exposure to 10 ppm[123]. In both investigations the cause of death was severe pulmonary congestion and hemorrhage. Five min. exposure to 130 ppm acrolein has been shown to produce reduced pulmonary compliance, resistance, and tidal volume in mice[124]. In guinea pigs, similar alterations of ventilation and pulmonary mechanics were seen after exposure to 17 ppm[125] for a few minutes. Studies of the effect of acrolein on the rate of mucocillary clearance have not been reported. However cessation of mucocillary transport and decrease of cilliary beat frequency have been demonstrated[126] suggesting that acrolein may adversely effect this pulmonary defense mechanism. Acute

exposure to acrolein at concentrations found in cigarette smoke (up to 90 ppm) have been shown disrupt pulmonary macrophage function in animals[127] and humans[128]. Thus in the absence acute severe pulmonary damage, acrolein exposure causes pulmonary toxicity by disrupting two major pulmonary defense mechanisms.

Lethal tracheal and laryngeal edema has been reported in rats exposed to 435 ppm acrolein for 10 min[129]. Necrosis and epithelial exfoliation in the nasal tract has been reported in a number of species after acute exposure to acrolein at concentrations ranging from 0.4 to 4.9 ppm[130,131,132].

Considerable variation in the severity of lesions of the lower respiratory tract has been observed following exposure to acrolein. High exposure concentrations (280 ppm) for brief periods (10 min.) in rats has resulted in destruction of the bronchial mucosa, pulmonary congestion and edema[133]. Severe pulmonary atelectasis, edema, and infiltration of inflammatory cells have been reported in mice exposed to 50 ppm acrolein[134]. Guinea pigs exposed to 2700 ppm acrolein for 1 min. developed severe hemorrhagic pulmonary edema. Animals that survived this exposure for a few days demonstrated granulation of the alveolar infiltrate and fibrosis reminiscent of ARDS[135].

Studies have shown that 75 % of inhaled acrolein is retained in the nose and upper respiratory tract[136] suggesting that this is the primary site of acrolein respiratory toxicity at low concentrations. However, acrolein also has been shown to adsorb readily to aerosol particles which has enhanced macrophage cytotoxicity[137]. Co-exposure of rats with acrolein and aerosol particles has been shown to cause a shift the site and severity of pulmonary lesions produced by acute exposure to 5 and 6 ppm acrolein alone[123,138]. Consequently the pulmonary toxicity

produced by acrolein exposure in fire atmospheres where particles are present may be more severe that normally produced by exposure to acrolein alone.

Many of the toxic effects of acrolein have been attributed it's reaction with critical sulfhydryl groups. Sulfhydryl groups present in proteins and peptides play important roles in the processes of living cells and deactivation of these groups can cause a variety of toxic effects, from disruption of metabolism, inhibition of cell growth, to cell death[139]. Acrolein also reacts with primary and secondary amines to form propenediamines. The reaction of acrolein with amino groups is slower and adducts formed are less stable than those formed with sulfhydryl groups. Nevertheless, reactions of acrolein with amino groups are responsible, in part, for some of the biological effects of acrolein[140]. Acrolein also has been shown to deplete respiratory mucosal glutathione thus disrupting pulmonary xenobiotic metabolism[141]. Regardless of the moiety involved, it is clear that the primary mechanism of acrolein pulmonary toxicity is binding with proteins.

Chemical Injury - Interactions of Smoke Components.

With a chemically complex atmosphere such as smoke, toxicological responses to given component in smoke most probably will be modified by other components in the smoke. There is ample evidence of additive and competitive interactions of smoke constituents. Synergistic interactions of smoke constituents is controversial[114]. Most of the studies of smoke component interactions have employed the strategy of exposing animals to surrogate smoke atmospheres composed of a few of the major smoke toxicants[142,143,144]. However, the effects of multicomponent mixtures which are more than the combination of a few common smoke gases have not been reported. The toxicity of mixtures of these gases and other constituents such as

organic vapors, reactive constituents, and/or particles is largely unaddressed[47]. Consequently it is difficult to rule out significant toxicological synergism between smoke components. Nevertheless, a number of studies of combinations of smoke toxins have shown complex interactive effects[145,146,147,148,149]. In addition to chemical constituent interactions, the effects of increased temperature and reduced oxygen tension have been shown to influence the toxicity of some smoke constituents[150]. Toxic smoke constituents which act by similar mechanisms would be expected to directly augment the action of one another, however there are few studies of this possible smoke constituent interaction. The augmentation of one another by toxic smoke components which act by fundamentally different mechanisms is subject to controversy. The irritancy effect of HCl which decreases respiratory rate has been shown to elicit a "protective effect" for CO induced incapacitation and death in rats[151]. Because CO and HCN interfere with the transport and utilization of O_2 respectively it might be expected that simultaneous exposure would elicit additive toxic effect. However, studies of co-exposure to CO and HCN have been equivocal. Higgins and colleagues[152] found no additive effect (lethality), whereas Smith[153] and Lynch[154] reported definite additive effect with regard to time to incapacitation and death. Similar controversy exists regarding co-exposure to NO_2 and CO, HF and CO, and a combination of acrolein and CO[155,156]. Carbon dioxide is a well known stimulant of ventilation, and one would expect that co-exposure of toxic smoke constituents with CO_2 would result in an increase in their toxicity due to increased deposition from increased ventilation. Inhalation of CO_2 increases blood hydrogen ion concentration which in turn stimulates ventilation; in humans, 2.5 % CO_2 can double minute ventilation[157]. The effect of increased ventilation would be expected to increase uptake of other smoke constituents that had not yet reached saturation limits.

Studies of the effects of simultaneous inhalation of CO_2 and CO (at concentrations well below saturation limits) have yielded conflicting results with respect to toxicity. Levin and colleagues[158] found that 2500 ppm of CO was twice as lethal to rats in the presence of 5% CO_2. Other investigators[159] found that there was substantial decrease in time to death from 6000 ppm CO when the atmosphere contained 4.5 % CO_2. However, neither Crane[160] nor Hartzell and Switzer[161] observed a change in lethality or time to incapacitation in rats exposed to atmospheres with similar respective concentrations of CO and CO_2. Despite the conflicting results and controversy regarding synergism there is evidence that interaction of smoke components with one another substantially effects the toxicity of individual components. Using the N-gas model, Levin[162] has successfully predicted the lethality of atmospheres containing 6 toxic smoke constituents (CO, CO_2, HCN, HCl, HBr, and NO_2) and low O_2.

Existing studies of smoke constituent interaction have focused on lethality and incapacitation measured by behavioral and neurological tests. Thus these studies do not provide information specific to smoke induced pulmonary disease. They also are limited with respect to evaluation smoke induced pulmonary disease by the fact that very few of these investigations have included aerosol particles as part of the exposure atmosphere. Aerosol particles are ubiquitous in combustion atmospheres and are found in many thermal degradation atmospheres. Exposure to carbonaceous aerosol particles alone has been found to elicit untoward pulmonary responses[163]. This and the fact that particles act as carriers for smoke vapor phase components causing changes in the expression of the toxicity of these components suggests that there is a fundamental gap in combustion toxicity data. Additional research is necessary to expand surrogate smoke models to

include aerosol particles and to employ these models to investigate the pulmonary effects of smoke exposure.

Chemical Smoke and Obscurants - Zinc Chloride

Zinc chloride ($ZnCl_2$) is a corrosive salt that is the primary ingredient in smoke bombs often used as an obscurant, for crowd dispersal and occasionally as a practice smoke in military and civilian fire-fighting exercises. Serious pulmonary injury typical of severe ARDS has been reported in victims of accidental exposure to smokes from these bombs[164]. Ten of 70 people died of respiratory failure within four days after exposure to a high concentration (estimated 33,000 mg/m_3 - zinc) of $ZnCl_2$ smoke following an explosion of smoke generators in a tunnel during a bombing raid in World War II[165]. Autopsy revealed severe pulmonary congestion and diffuse alveolar edema. The smoke generated was composed mainly of $ZnCl_2$, however other constituents such as zinc oxide could have attributed to the deaths of these individuals. Milliken and colleagues[166] reported the death of fireman 18 days following accidental inhalation of $ZnCl_2$ smoke during a fire-fighting demonstration. The victim's alveoli were completely obliterated by fibrosis and right ventricular hypertrophy was taken to be a sign of pulmonary hypertension. Two soldiers accidentally exposed to $ZnCl_2$ smoke during training died from severe pulmonary damage within 32 days of exposure. As is typical of ARDS, the onset pulmonary symptoms was delayed. Both victims reported feeling in satisfactory condition as late as 10 days after the exposure. Autopsy revealed diffuse obliteration of the pulmonary microvasculature, wide spread occlusion of pulmonary arteries, and extensive interstitial and alveolar fibrosis[167,168]. Several other investigations[169,170,171] have reported a variety non-lethal of pulmonary effects in humans following acute accidental exposure to $ZnCl_2$ smoke. This includes dyspnea, decreased vital capacity, chest

pain, bilateral diffuse infiltration, and acute pneumonitis. In one of these studies[169] the concentration of $ZnCl_2$ was estimated to be 4,075 mg/m^3.

Subchronic exposure (1 hr/day, 5 day/week, 3 weeks) to $ZnCl_2$ smoke at much lower concentrations (119 to 127 mg/m^3) has been shown to cause focal alveolitis, vascular coagulation, infiltration of macrophages and pulmonary fibrosis in guinea pigs[172]. As with the human studies the $ZnCl_2$ smoke atmospheres also contained some zinc oxide. Two to three hours exposure of rats and guinea pigs exposed for two to three hr to 2.2 mg/m^3 zinc oxide has been shown to cause increased levels of a β-glucuronidase in BAL fluids suggesting change in pulmonary macrophage function as well as titer that is often associated with ALI/ARDS[173].

$ZnCl_2$ is extremely hygroscopic and is thought to form hydrochloric acid and zinc oxychloride on contact with mucous membranes[171] causing immediate cytotoxicity. Zinc also has been shown to be retained in the lung[173]. Consequently displacement of calcium in calmodulin zinc and binding to other proteins[174] cannot be discounted as the possible mechanism of the delayed pulmonary toxicity seen in victims of to $ZnCl_2$ smoke exposure. Inhaled zinc oxide has been shown to elicit both release of histamine in the respiratory tract and to cause sensitization of the airways. It has been suggested that $ZnCl_2$ may elicit a similar immunological response[175].

PULMONARY TOXICITY OF CHEMICAL MUNITIONS

There are several general categories each of which are designed to elicit effects to suited specific military aims[176]. These categories include; riot control agents, choking agents, blood agents, nerve agents, incapacitants, and blister agents. Agents found in each of these categories

have been shown to cause respiratory and pulmonary effects which often are secondary to the principal (intended) effect.

Riot Control Agents

Riot control agents (lacrimatory agents) have short effect and are designed to disrupt purposeful behavior at a specific site. Generally they are potent irritators mucous membranes causing pain and copious secretions. At higher doses, distal portions of the respiratory tract may be affected.

Chloroacetophenone (CN)

Synonyms for CN ($C_6H_5COCH_2Cl$) include "tear gas", Mace and Cap. Prisoners sprayed with CN aerosol during a prison riot showed signs typical of exposure to this agent also manifested numerous symptoms of pulmonary toxicity[177]. In addition to a burning sensation of eyes, nose, and throat, these prisoners suffered rhinorrhea, dyspnea, pharyngeal edema, and cough which persisted for 1 to 2 days. Although lacrimatory symptoms generally abate within 10 to 20 min. on cessation of exposure to CN, and pharyngeal edema may persist for several days. Short term exposure (10 min) to 140 ppm has been shown cause lethal pulmonary edema within 12 hrs. of exposure[178,179,180]. Survivors of the initial edema and intraalveloar hemorrhage show signs of necrosis of the respiratory mucosa and formation of pseudomembranous exudates. Monkeys exposed to 280 ppm CN for 5.5 min. showed severe hemorrhagic edema at 24 to 72 hr. In surviving animals the acute pulmonary edema completely resolved within 30 days[181].

CN is thought to act, primarily, as an alkylating agent combining sulfhydryl containing enzymes and tissue proteins. Therefore cross linking of protein is the most probable cause of the

pulmonary effects of CN exposure[182]. Lacrimation and mucous hypersecretion caused by CN exposure has been attributed to rapid non-competative binding of CN to cholinesterase[183].

Chlorobenzylidene (CS)

CS ($C_{10}H_5ClN_2$) exposure causes copious rhinorrhea and salivation accompanied by dyspnea and coughing at higher doses. These symptoms abate within 30 min. of cessation of exposure[184]. Although no deaths have been reported from CS exposure, exposure to high concentrations have been shown to produce respiratory distress, cyanosis, and pulmonary edema. Pulmonary function studies of victims of CS exposure have not revealed significant persistent pathophysiology[185], however exacerbation of underlying asthma and chronic bronchitis has been shown[186]. A causal relationship between asthma and CS has not been established. Monkeys exposed to 600 to 1,000 ppm CS for 10 min. have shown bronchiolitis and edema which resolved but produced emphysematous changes in lung parenchyma[187].

Like CN, CS also acts by alkylating sulfhydryl groups in enzymes and proteins. CS has also been shown to bind specifically to glutathione and to inhibit lactate dehydrogenase as well as other nucleophilic compounds[188]. Both reactions are possible mechanisms of CS pulmonary toxicity.

Diphenylaminochlorarsine (DM) and Dibenzoxazepine (CR)

Not much is known about possible respiratory effects of DM and CR exposure other than pronounced irritation of upper airways mucosa. One accidental death due to short term (5 to 10 min.) exposure to 1130 to 2260 mg/m^3 DM aerosol has been reported[179]. Animal studies[181] have shown that exposure to high concentrations of DM causes death within 24 hr. of exposure due to

hemorrhagic pulmonary edema. No long term respiratory effects have been shown after exposure to CR aerosols.

Choking Agents

Choking agents designed to induce severe incapacitation or death due to respiratory effects. Onset of symptoms may vary from immediately upon contact to several days post exposure. Primarily examples include phosgene (CG), diphosgene (DP), chlorine (Cl), and chloropicrin (PS). Phosgene and chlorine toxicity have been addressed. A mole of DP in aqueous solution produces two moles of CG, and therefore the toxicity of DP is identical to that of CG.

Chloropicrin (PS)

Chloropicrin (CCl_3NO_2 - "vomiting gas", green cross) also is used as an insecticide, sterilizing agent, and because of its strong odor has been used as a warning agent in other fumigants. Thermal decomposition of PS produces phosgene, various oxides of nitrogen, chlorine gas, and CO. At low concentrations (15 ppm) the effects of PS include cough, lacrimation, rhinorrhea, and vomiting. At lethal concentrations (119 ppm), short term exposure (30 min.) induces cyanosis, dyspnea, and signs of pulmonary edema with death occurring in a few hrs[189]. Survivors of acute exposure show persistent dyspnea and cyanosis, however other long term effects have not been reported. In animals, high concentration exposures produce pulmonary edema with a characteristically high fibrin content. Focal bronchial occlusions with inflammatory cells appear within hrs. of exposure[190]. The mechanism of PS pulmonary toxicity is not known, however PS has been shown to be corrosive to skin and it is assumed that the effect on pulmonary

cells is similar. Vettorazi[191] has demonstrated methemoglobin formation as a result of PS exposure, however the clinical significance of this is uncertain.

Blood Agents

These agents are transported by the circulatory system and function by blocking oxygen transport or cellular respiration. Typical blood agents include cyanide (AC) and cyanogen chloride (CK). AC pulmonary toxicity has been addressed and CK is rapidly metabolized on inhalation to cyanide, thus the toxic effects of CK can be attributed to AC[192].

Nerve Agents

Nerve agents affect cholinesterases and therefore neurological control of control of bodily functions. The primary toxicity of these organophosphate (OP) esters is the paralysis of the respiratory muscles through inhibition of cholinesterases[193]. Respiratory muscle paralysis will persist until restoration of the cholinestrases or death ensues. Other clinical sequelae include muscle twitching, seizures, and vomiting. Although there are insufficient data to allow assessment of the effects of OP agents on pulmonary biochemical function or defense mechanisms there are some anecdotal reports of OP induced pulmonary toxicity. Thermal degradation and combustion of many of the OP agents produces a number of well known pulmonary toxins such as cyanide, oxides of phosphorous, sulfuric acid, and HF. Therefore heat is not recommended as a method of decontamination and combustion of OP agents poses a significant risk of pulmonary toxicity.

Although research has been conducted to investigate the environmental persistence of aerosol forms of OP agents, little is known about the potential pulmonary toxicity of OP agent aerosols.

Vesicants

Blister agents were primarily developed for their dermal toxicity and incapacitation due to vesicant damage to the skin. However most vesicants also induce severe respiratory injury. Examples of vesicant agents include , lewisite, phosgene oxime, and sulfur and nitrogen mustard.

Lewisite

Production of lewisite results in a mixture of three similar arsinicals known as lewisite I, II, and III {$ClCH{=}CHAsCl_2$, $(ClCH{=}CH)_2AsCl$, and $(ClCH{=}CH)_3As$ respectively}. Of these three compounds lewisite III has little effect on either the skin or respiratory system. The odor threshold concentration is far below toxic concentrations and therefore lewisites have an intrinsic warning property. They can be delivered either as a vapor or in aerosol form when stabilized with methyl methacrylate. The lethal concentration-time product for inhalation is 1200 $mg \cdot min/m^3$. Accidental human exposures in enclosed spaces have been shown to produce immediate rhinorrhea and irritation of the upper respiratory tract. No human pathologic data are available.

Exposure of dogs to 2800 mg/m^3 lewisite for 30 min. has been shown to cause acute pulmonary vascular coagulation, and pulmonary edema with pseudomembrane formation. Necrotic, fibrinous mucosal membranes detach resulting in obstructive atelectasis and emphysema[197,198]. In these same animals, degenerative lymphatic changes and fatty necrosis of the liver also was observed, however these effects were not considered to contribute to deaths from lewisite exposure. The mechanism of lewisite pulmonary toxicity is not well understood.

Phosgene oxime (CX)

Very little has been reported regarding the pulmonary toxicity of CX (CCl_2HOH). Topical absorption in one human subject produced dyspnea, and was reported to be an early sign of

pulmonary edema[199]. However this was not substantiated by further radiological or physiologic evidence. However, exposure of dogs to 1.5 to 2 g/m^3 concentrations of CX for 30 min. has been shown to produce lethal non-cardiogenic edema[200].

<u>Nitrogen</u> (HN_1, HN_2, HN_3) <u>and Sulfur Mustard</u> (H, HD, HQ, HT)

With exception dose response relationships the there is little difference between the toxic effects of nitrogen and sulfur mustards. Nitrogen mustards are not as chemically stable as sulfur mustards and therefore have not been used as extensively. Much more is known about the effects of sulfur mustard.

Sulfur mustard (SM - used here for convenience) has numerous synonyms, including Yperite, Yellow Cross, and mustard gas as well as the NATO designators listed above. Although the terms H, HD, HQ, and HT are often used interchangeably they have discrete meaning which refers to the manufacturing process, physical form, and relative purity. Chemically SM {$S(CH_2CH_2Cl)_2$ is referred to variously as:

di(2-chloroethyl)sulfide, 1,1'-thiobis[2-chloroethane],

bis(2-chloroethyl)sulfide,

bis(β-chloroethyl)sulfide,

2,2'-dichlorodiethyl sulfide,

β – β-dichloroethyl sulfide, and
1-chloro-2-(β-chloroethylthio)ethane[20].

The death rate from SM exposure during the first world war was approximately 2% among disciplined troops with gas masks, whereas the death rate in those without masks was 50%[201]. Most of these fatalities occurred generally during the second or third day after exposure from secondary bronchopneumonia[202]. Although SM can cause death in several ways, the

majority (80 to 90 %) of fatalities were due to respiratory injury. Autopsy findings in victims exposed to very high concentrations of SM revealed severe injury occurred throughout the respiratory tract resulting in congestion and hemorrhagic edema[203, 204]. The high frequency death due to serious respiratory tract injury after SM exposure was confirmed by examination of casualties of the Iraq-Iran war. Typical pulmonary complications in these victims included hemorrhagic tracheitis, pulmonary edema, and purulent bronchitis requiring oxygen therapy and artificial ventilation[205,206,207,208]. Death attributed to severe respiratory insufficiency with severe airways obstruction, and pulmonary edema occurred within a few weeks of exposure[209]. The concentration-time product lethality index (LCt_{50}) for SM inhalation is 1,000 mg·min/m^3 [210]. However, mild respiratory symptoms which persisted for several days have been reported[211] in individuals exposed to 12 mg·min/m^3.

The clinical picture of SM induced respiratory tract injury is one of acute damage to tissue followed by inflammation and the complications of sepsis. Detailed accounts of the pathogenesis of acute lung injury at the microscopic level are not available. The most complete descriptions of SM induced lung pathology come from a review data from WWI gas victims by Pappenheimer[204] and the reports on Iran-Iraqi war gas casualties by Hochmeister and Vycudilik[212]. In most cases, victims died within several weeks from the complications of secondary infection, SIRS, and multiple organ failure. The cases that died within a few days present the most accurate picture of acute lung injury stemming from the effects of SM. The primary lesions were found in the upper airways (larynx, trachea, and bronchi), with fewer lesions found in the pulmonary parenchyma. The presence of fibrinous pseudomembranes containing neutrophils, macrophages and detached epithelial cells was a common observation. Evidence of mucous hypersecretion also was common. Interstitial edema was prevalent with some alveolar histiocytosis and edema being

observed. Severe alveolar flooding appeared in only a few of the victims that died very early. It was assumed that these victims were exposed to very high concentrations of SM[204] in which there was greater penetration in the lung. Although pulmonary capillaries were congested and distended there were no indications of damage or degeneration of the vascular endothelium. Emphysema that was presumably compensatory for acute airways obstruction also was observed.

Persistent pulmonary effects in survivors of SM exposure similar to those found in survivors of acute ARDS have been reported. Approximately 12 % of the British soldiers gassed with SM in WWI received disability compensation based on diagnosis of bronchitis, emphysema, and asthma. However epidemiological studies of the exposures and subsequent respiratory disability are sketchy[213,214], and available data are complicated by that influenza co-morbidity that was a major complication in many of these casualties. Follow up of more than 200 Iranian soldiers provides a more thorough evaluation of the persistent respiratory effects of SM exposure[215,216,217]. About one third of these victims experienced persistent (2 years post exposure) pulmonary problems which included chronic bronchitis, laryngitis, recurrent pneumonia, and bronchiectasis.

Although it is well known that SM produces lesions in the respiratory tract after inhalation there have been few studies which systematically examine respiratory tract injury in animal models. The majority of the studies were conducted prior to 1925. The microscopic effects SM exposure in rabbits show lesions similar to those found in human exposure victims[218]. However this study provides limited information about SM exposure response characteristics because of a large variation in exposure concentration time product and the complications of secondary infection. The major findings of this study were necrosis of the upper respiratory tract mucosa,

vascular congestion, interstitial and alveolar edema, focal atelectasis, and formation of hyaline membranes. These lesions progressed down the respiratory tract as a function of increasing exposure concentration time product. In severe cases, hemorrhagic edema with plugging of the bronchioles by infiltrate was observed. Winternitz and Finney[203] reported similar findings in dogs that died within 3 days of exposure and that also did not have evidence of secondary infection. Typical findings were near complete destruction of the epithelia and severe alveolar flooding. The alveolar exudate was fibrinous and contained red blood cells as well as leukocytes. These lesions were caused by exposures with a LCt as low as 100 $mg \cdot min/m^3$. Vocci and colleagues[219] conducted studies with dogs, pigeons, and small laboratory rodents and concluded that dogs were more sensitive to SM shown by an increased frequency and severity of lower respiratory tract lesions. Other investigators found that SM exposure produced lethal systemic toxicity in rodents with relatively little damage to the lower respiratory tract[220,221].

Despite the importance of respiratory tract lesions in SM induced mortality, there are no mechanistic studies of the mechanisms SM induced pulmonary irritation, inflammation, and destruction. Several hypotheses have been put forth the mechanisms and pathogenesis of SM induced lung injury, all of which are in need of further investigation. The massive influx of leukocytes, and monocytes found in the lungs of victims dying shortly after SM exposure has led to speculation that release of proteases and oxidants by these cells coupled with depletion of the protease inhibitors due to serous cell cytotoxicity leads to a protease-antiprotease imbalance which favors tissue destruction[222]. There is evidence to suggest that SM induced pulmonary edema may be neurogenic in origin, mediated through increase in membrane permeability caused by release of vasoactive peptides such as substance P[223]. This, however, could be a secondary

response due to stimulation of sensory nerve fibers subsequent to destruction and loss of pulmonary epithelia.

There are several hypotheses for SM cytotoxicity. SM has been shown to inhibit glycolysis causing cell death and therefore acute tissue injury[224]. SM is also a potent alkylating agent capable forming adducts with proteins, membrane phospholipids, and other macromolecules such as DNA and RNA. Although SM is hydrolyzed rapidly, the alkylation reaction rates with these and other biologically important molecules are sufficiently rapid to contribute to SM cytotoxicity[20]. High doses of SM have been shown to deplete glutathione (GSH) leading to the hypothesis that SM cytotoxicity may be due to reduction of cellular protein thiol levels leading to cytotoxic increase in cytosolic Ca^{2+} levels[225]. Another result of GSH depletion may be membrane lipid peroxidation[227]. There is some evidence to suggest that SM alkylation of DNA causes activation of poly (adp-ribose) polymerase (PADPRP) enzyme leading to inhibition of glycolysis through depletion of NAD^+. This would stimulate of the release of proteolytic enzymes[227]. Prolonged stimulation of the release of proteolytic enzymes is hypothesized to be the cause of the delayed cytotoxicity associated with SM injury. The PADPRP and other hypotheses all offer plausible explanations of the mechanisms of SM induced pulmonary disease, however without further experimental clarification no single hypothesis can be considered definitive. It is likely that all the postulated mechanisms of injury play a role in SM induced pulmonary damage[20].

The effects on SM vapor interaction with aerosol particles on SM inhalation toxicity have not been thoroughly investigated. However, there is limited information on the relative toxicity of so called "dusty mustard" an aerosol formulation of SM. The deployment of vesicant agents in dusty form was shown to increase environmental persistence, enhance dermal toxicity, and

possibly favor pulmonary toxicity due to deeper penetration into the respiratory tract when inhaled[228].

RESEARCH MODELS OF ALI/ARDS, AND SMOKE INHALATION TOXICITY

Models of ALI/ARDS

A systematic evaluation of the pathogenesis, and mechanisms of inhalation ALI/ARDS requires the exploitation of animal models of the disease. Likewise, a systematic characterization of the potential for exposure atmospheres, particularly complex ones, to induce ALI/ARDS also requires a well characterized animal model of the disease[228]. At present there are several animal models of ALI/ARDS which simulate many aspects of the disease as it occurs in humans. However, none of current animal models of ALI/ARDS exploits inhalation exposure to whole or surrogate smoke to induce the disease. Existing research models of smoke inhalation toxicity that simulate exposure to whole or surrogate smoke either do not or are not suited to systematic evaluation of the mechanisms pathogenesis of inhalation ALI/ARDS. Consequently, there are still several research challenges to be met in both the characterization of inhalation ALI/ARDS pathogenesis and the identification of the principle toxicants, typical of smokes, that are involved in the process[229].

An ideal animal model of smoke induced ALI/ARDS would require well controlled exposure to smoke or a suitable surrogate atmosphere and would faithfully reproduce the pathophysiology of the disease as it occurs in humans[230]. There are several well known models of ALI/ARDS which although useful do not pertain to inhalation injury. The first and most widely

recognized animal model of ALI/ARDS is the oleic acid (OA) model of Ashbaugh and Uzawa[231]. In this model, OA is administered parenterally, and is useful for simulating ALI/ARDS without sepsis and relies upon the inflammatory response to initiate the alveolar damage. Unfortunately this model in an unlikely paradigm for any etiology of ALI/ARDS except possibly that of fat embolism. The lipopolysaccharide (LPS) moiety of bacterial endotoxin has been injected in variety of animal species to mimic circulating endotoxin and initiate the sequence of events leading to an increase in pulmonary microvascular permeability and endothelial damage associated with ALI/ARDS[232,233]. The pulmonary edema caused by administration of LPS mimics early ALI/ARDS well, in particular that caused by SIRS and sepsis. The disadvantage of the LPS model is that it does not simulate direct parenchymal injury in a manner similar to inhalation ALI/ARDS. Although LPS has been administered by inhalation in an aerosol form. Several different chemicals have been administered to different species by a variety of exposure routes to induce pulmonary toxicity reminiscent of ALI/ARDS. Among the most well known are the antineoplastic drug bleomycin and the herbicide paraquat. Both of these chemicals have been shown to cause acute injury to the alveolar/capillary membrane which progresses through an infiltration phase to fibrosis. Both have been shown to effect numerous cell populations, mediators, aspects collagen metabolism, and surfactant integrity in the lung after injection, ingestion and inhalation[234-239]. Although both of these models mimic the pathogenesis and are possible etiologies of ALI/ARDS, neither are particularly relevant to inhalation ALI/ARDS as it relates to smoke exposure. Likewise, the same general lack of etiologic and possible pathogenic similitude to smoke inhalation ALI/ARDS applies to several other well known models of the disease. This includes lung injury induced by toxins such as phorbol myristate[240],

alpha-napthylthiourea[241], and N-nitroso-N-methylurethane[242]. These three chemical models of ALI/ARDS usually are produced by intravenous injection and therefore epithelial damage is usually secondary to endothelial damage. Consequently it is difficult to relate them to smoke induced lung injury where epithelial damage is most likely the primary insult. Exposure to high oxygen tension atmospheres, to O_3, and to NOx are representative of inhalation models of ALI/ARDS. The former two both produce extensive acute pulmonary edema accompanied by an influx of leukocytes which is followed fibrosis. Damage caused by hyperoxia and O_3 is possibly mediated by the synthesis and release of leucotoxin from stimulated leukocytes[243]. However, oxygen toxicity is most likely not a factor in ALI/ARDS produced by inhalation of smoke or surrogate smoke atmospheres. Many aspects of NOx pneumotoxicity do not correlate well with the pathogenesis of ALI/ARDS.

Models of Smoke Inhalation Toxicity

Both combustion (flaming) and pyrolysis (non-flaming) atmospheres are highly complex. In addition to physical and chemical complexity fire atmospheres are dynamic. Primary chemical products interact with themselves and available surfaces producing multiple generations of chemical species available for inhalation. Thus the rapidly changing quality of fire atmospheres adds to the enormous complexity of fire environments. Relatively few studies have been performed that profile the changes and toxic products of real fire atmospheres, probably because there is no such entity as a typical fire[244-255]. Nevertheless, as noted previously, there are certain common toxic chemical constituents that are typical of the majority of fire atmospheres. In light of this complexity, two fundamentally different approaches have been taken to investigate smoke inhalation toxicity. One approach is to expose animals to products generated by combustion and

pyrolysis of bulk materials, controlling the "fires" and delivery of the products as well as is technically feasible. The latter being no mean feat. An alternative approach has been to create surrogate smoke atmospheres which are controlled mixtures of typical fire atmosphere constituents. Each approach has distinct advantages and disadvantages.

A number of differing approaches have been taken to develop research models of inhalation injury using "real" smoke. Studies have been conducted in unanesthetized, spontaneously breathing animals without endotracheal tubes[256-260]. In these studies, delivery of smoke to the lungs is modified by animal reflexive change in breathing pattern and by interception of some smoke constituents, primarily aerosols, in the proximal airways. The latter is of particular concern when small laboratory rodents have been used as experimental subjects. Several studies have been conducted using whole smoke exposure of animals which have been anesthetized to eliminate unpredictable modification of dose by change of breathing pattern. Endotracheal tubes have been used in some studies to eliminate deposition of smoke constituents in upper airways[261-263]. Although the use of endotracheal tubes may simulate naso-oral breathing in humans under stress the effects of intubation confound experimental results. Other investigators[264-266] have avoided the use of endotracheal tubes so that the contribution of heat and chemical damage to upper airways was part of the overall assessment of lung injury. Some experimental models have employed endotracheal tubes and mechanically controlled ventilation in attempt to exert more control of smoke dose[267-269]. The focus of most of these investigations regardless of technical approach has been upon examining the dynamics of extravascular lung water (EVLW), physiological responses, and pathology. Very few of these studies have investigated biochemical aspects of the inflammatory response and surfactant response. Most of

these and similar classic studies[270-274] of EVLW dynamics and physiologic response have been conducted using either sheep or dogs. Despite the valuable contributions of these studies to an understanding of smoke induced lung disease, there are two major limitations to use of these type of investigations for systematic investigation of the pathogenesis and mechanisms of smoke induced ALI/ARDS. First, because of the aforementioned chemical and dynamic complexity of smoke it is extremely difficult to perform dose/response investigations. Second, because of their reliance on larger animal species if is not technologically and financially feasible to expose large numbers of animals. Extensive investigation of several biochemical and physiological endpoints in a serial manner is not possible.

Clark[228] expressed one of the fundamental ideas behind the use of surrogate smoke atmospheres to investigate smoke inhalation toxicity quite well. "In order to make experiments clinically relevant and the severity of the lung damage inflicted by the products of combustion proportional to the duration of exposure, the smoke needs to be generated in a standard way (so that its characteristics are reproducible. The environmental contaminants responsible for anoxia: elevated cyanide, carbon monoxide, and reduced oxygen should permit survival after exposures of short duration." The use of surrogate smoke atmospheres permit a more controlled delivery of mixtures of toxic smoke constituents and therefore are amenable to the conduct of dose/response investigations. Although the number of "typical", principle toxins identified in smoke is relatively limited the major drawback of this approach is that the atmospheres are more removed from real fire scenarios and exposures. Regardless of this drawback, numerous investigations of smoke toxicity have been conducted using the surrogate smoke approach[60-63,67-69,92,114,143-152,155-163]. The use of the surrogate smoke has led to the development of sophisticated mathematical models for

quantification of dose for mixtures of toxic smoke constituents. These models have been applied to the prediction of smoke inhalation toxicity of atmospheres based on quantitative analysis of a few smoke constituents. Two of the more well known are the fractional effective dose (FED) model[149] and the N-gas model[162]. Both the FED and N-gas models have been used to estimate the toxicity of a variety of fire atmospheres. By-in-large, this approach has not been applied to the examination or prediction of smoke induced pulmonary injury. Relatively few surrogate smoke investigations have focused upon pulmonary injury[69,275,276]. These studies were not predictive nor were the atmospheres very complex chemically. A principal drawback of most surrogate smoke investigations is that they have not included aerosol particles as a fundamental part of the mix. Neither the FED model nor the N-gas model of smoke toxicity includes aerosol particles. in light of the evidence that particle vapor interaction can alter the toxicity of various components of smoke and that aerosol particles themselves can pose a significant pulmonary toxicity risk (both chemical and mechanical), the exclusion of particles from these models limits their effectiveness as predictors of pulmonary toxicity.

DISCUSSION

Much has been discovered about ALI/ARDS in the 30 years since it was first described. Yet is evident that much yet to learned, particularly about risk factors associated with inhalation injury. Naval personnel are significant risk of ALI/ARDS from a variety of potential inhalation hazards. The most probable risks are associated with the inhalation of the byproducts of combustion and pyrolysis and to some extent exposure to CW agents. Of these two risk

categories exposure to smoke represents the greater risk. Larger numbers of personnel are at risk of smoke exposure at a higher probability under a wider variety of operational circumstances. Personnel at risk for ALI/ARDS from combustion and pyrolysis atmospheres are also may be subject to a lesser degree of preparedness. Obviously a war fighting scenario poses the most cause for concern over potential CW exposure. It also allows the most opportunity for preparedness. Never-the-less, the potential for exposure of large numbers of minimally prepared personnel to CW agents by terrorist action can not be overlooked. Recent incidents in Japanese mass transit systems serve as a grim reminder of this fact. Despite this possibility the principle risk concern remains exposure to fire atmospheres. Although the remaining discussion will focus on aspects of the smoke inhalation risk, the principles discussed apply equally well to risk associated with CW inhalation.

The nature of the inhalation health risk concerns over smoke inhalation has changed with the advent of newer and greater general use of more "exotic" materials of construction. A prime example is the reliance on plastic materials such as PVC where once metals were common place. In many instances the present protective strategies and devices are not adequate to the task with these newer types of smokes. In addition to changing chemical constituency of smoke atmospheres other fire risk factors also are receiving more notice. There is a wider recognition that potentially hazardous exposures are not necessarily limited to victims in the immediate vicinity of a fire or just to fire-fighting personnel. Davies[229] noted, in a recent outline of objectives for fire and smoke inhalation injury research, that there apparently is an increasing risk to personnel located in the surrounding environment. This takes on particular significance in a shipboard setting where escape from smoke atmospheres may not be possible.

Clark[238] recently formulated a synopsis of the smoke exposure-inhalation injury paradigm, listing numerous interactive variables which affect the outcome of smoke related lung injury. Interaction of variables further complicates the picture of smoke inhalation injury. In general, most of the variables in smoke inhalation scenarios can be outlined as such:

A. Smoke
    1. Fire conditions
        a. Fuel (rarely single or homogeneous).
        b. Heat production rate.
        c. Suppression or absence thereof.
    2. Combustion Products
        a. Thermal energy.
        b. Particles
        c. Toxic gases and vapors.
        d. Physical and chemical interaction.
        e. Irritating and anesthetizing properties.
        f. Density.
    3. Movement and control
        a. Space - confinement.
        b. Ventilation.

B. Victim
    1. Location
    2. Physical condition
        a. age.
        b. sex.
        c. health status.
        d. cognitive status (intoxication).
    3. Detection of hazard
        a. vision.
        b. decision, behavior.
    4. Dose
        a. exposure time.
        b. activity - respiratory rate, depth, and pattern.
        c. relative concentration.

C. Anoxia
    1. Degree
    2. Duration
    3. Therapy
    4. Consequences

D. Burn - absence or presence
    1. Before therapy - severity, extent, location, and duration of hypotension.

2. After therapy - resuscitive variables, changes in pulmonary microvascular fluid and oncotic pressure, drugs, anesthesia, aspiration, sepsis (primary - lung, secondary - burn wound), and pulmonary embolus.

E. Pulmonary Obstruction
  1. Level
  2. Degree
  3. Duration untreated
  4. Complications of treatment

F. Respiratory Failure
  1. Degree, location, injury homogeneity
  2. Site of injury
     a. epithelial.
     b. endothelial.
     c. surfactant.
     d. combinations of a,b,c.
  3. Mechanism of injury
     a. direct.
     b. products of white blood cells - cytokines.
     c. eicosanoids.
  4. Consequences
     a. pulmonary mechanics.
     b. lung fluid balance.
     c. gas exchange.

H. Recovery - With and without residual effects.

In simple terms this an outline of the complex interactions that occur between smoke and the victim. This synopsis makes it clear that it is improbable that research efforts to completely understand smoke induced ALI/ARDS will control or account for all the pertinent variables and their interactions. Never-the-less numerous avenues of research can and should be engaged in to further our understanding of ALI/ARDS related to smoke inhalation. Among the suggested lines of investigation are studies which broaden our understanding of which particular materials in smoke cause pulmonary injury. Focus needs to be placed on the pathogenesis of ALI/ARDS after smoke inhalation to identify points in the cascade of events which may broken, prevented, or which represent points opportunity for intervention. Smoke inhalation injury research needs, according to Clark[238], include investigations in "experimental animals with burns alone, smoke

inhalation injury with defined smoke alone, and the injuries combined." Furthermore, "in order to make experiments clinically relevant and the severity of the lung damage inflicted by the products of combustion proportional to the duration of exposure, the smoke needs to be generated in a standard way (so that it's characteristics are reproducible)". These two statements reflect, in part, the fundamental approach of a Naval Medical Research Institute Detachment/Toxicology (NMRI/TD) research program to investigate the pulmonary toxicity of smoke and other complex atmospheres. One of the essential features of the NMRI/TD research program is the use of surrogate smoke atmospheres composed of typical smoke constituents (including particles) that can be generated consistently, characterized thoroughly, are well controlled, and thus are reproducible.

Recent advances in understanding of the victim side of the smoke + victim paradigm for smoke inhalation injury have suggested new approaches to the investigation of ALI/ARDS. A systematic investigation of the mechanisms, pathogenesis, and outcomes of smoke induced ALI/ARDS needs to be undertaken. This requires the exposure of adequate numbers of animals so that various aspects of ALI/ARDS pathophysiology can be examined over time. Larger animal models (ovine and canine) of smoke inhalation injury cannot be exposed in sufficient quantity without prohibitive cost and extensive priori technological development. The selection of smaller laboratory animal species (rodents) for smoke induced ALI/ARDS studies satisfies the need for exposure of large numbers of test subjects. Historically one of the major drawbacks of utilizing small rodents for inhalation studies involving aerosols has been the differences in aerosol particle deposition pattern between rodents and humans. Because of the anatomy of the nasal passages and differences in basic breathing pattern (rodents are obligate nasal breathers) aerosol

particles tend to deposit higher in the respiratory tree of rodents. This fundamental difference in aerosol deposition has obfuscated extrapolation of results of inhalation studies using rodents to human risk assessment. However recent developments in aerosol deposition modeling[277,278,279,280] and lung structure modeling[281] have alleviated many of the difficulties in the extrapolation process. Non-phenomenological, predictive models of aerosol deposition based physiological and aerodynamic principles will permit more accurate predictions of human aerosol deposition and clearance from animal data. These models are not only crucial to the extrapolation process they are crucial to the conduct of dosimetric studies required for a systematic investigation of smoke induced ALI/ARDS.

The clarification of the ALI/ARDS disease spectrum and definition(s) agreed upon by the AECCA focused primarily on clinical and epidemiological issues. However, all of the pathophysiologic and clinical indices and most of the biochemical markers diagnostic of ALI/ARDS have correlates in small animal assays of pulmonary function. Therefore, the AECCA's definitions can modified and used to establish response criteria for dosimetric studies of smoke induced ALI/ARDS in small animals.

Small animal models of smoke induced ALI/ARDS are essential for numerous reasons. The identification of risk factors in combustion and pyrolysis atmospheres has been discussed. These models also are required for a systematic evaluation of novel methods and approaches to treatment of this family of diseases. The need for such a system of evaluation is emphasized by the widely held view that the utilization some conventional respiratory disease treatment protocols may have been detrimental to ALI/ARDS victims. Systematic evaluation methods also are required to develop new and more effective means to protect personnel at high risk. The

development of more effective personal protection may be accompanied by the development of systems in which data from atmospheric sensors can be coupled with rapid access to an appropriate lung injury risk data base so that operational risk benefit decisions can be made in real time.

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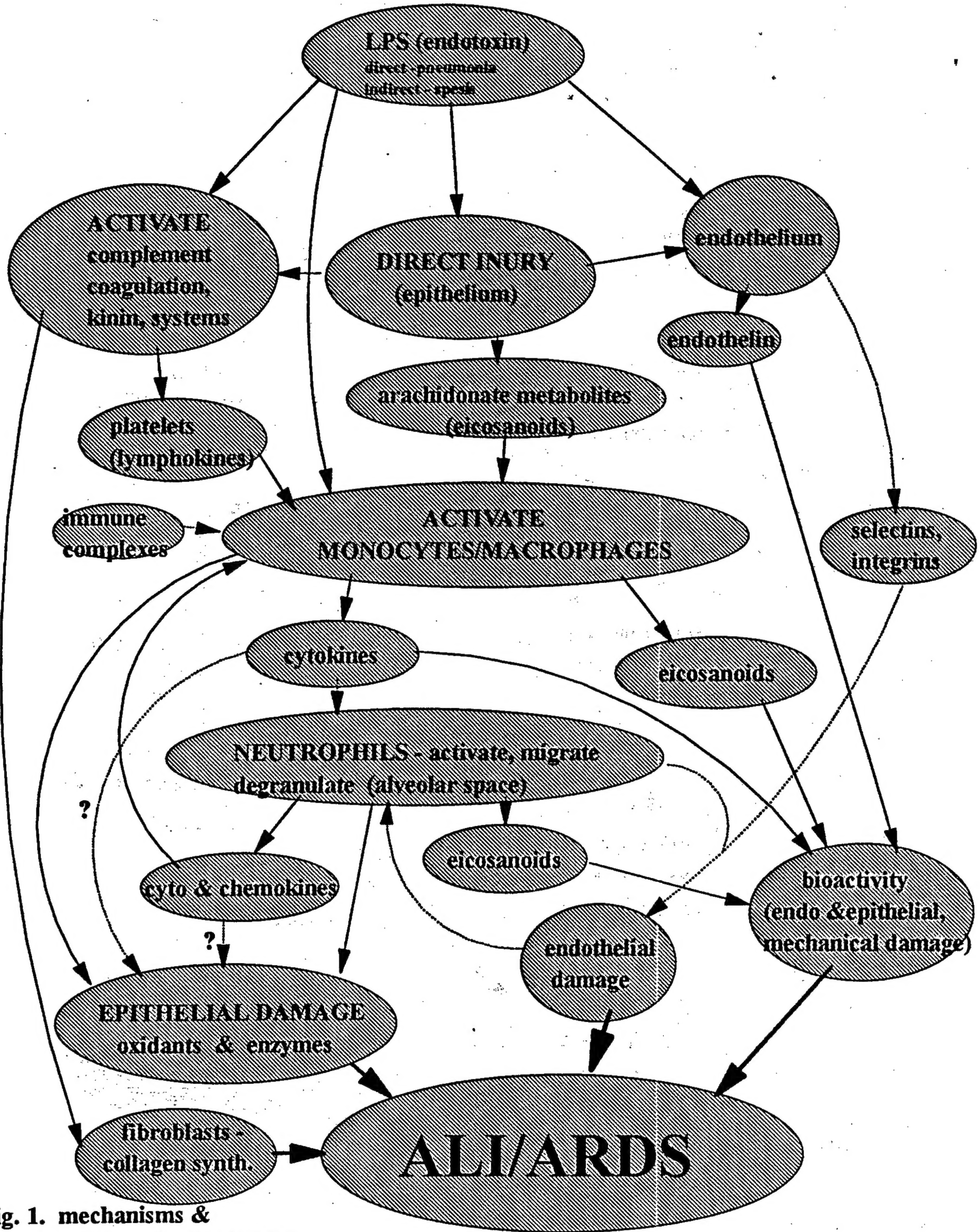

Fig. 1. mechanisms & mediators in septic ALI/ARDS

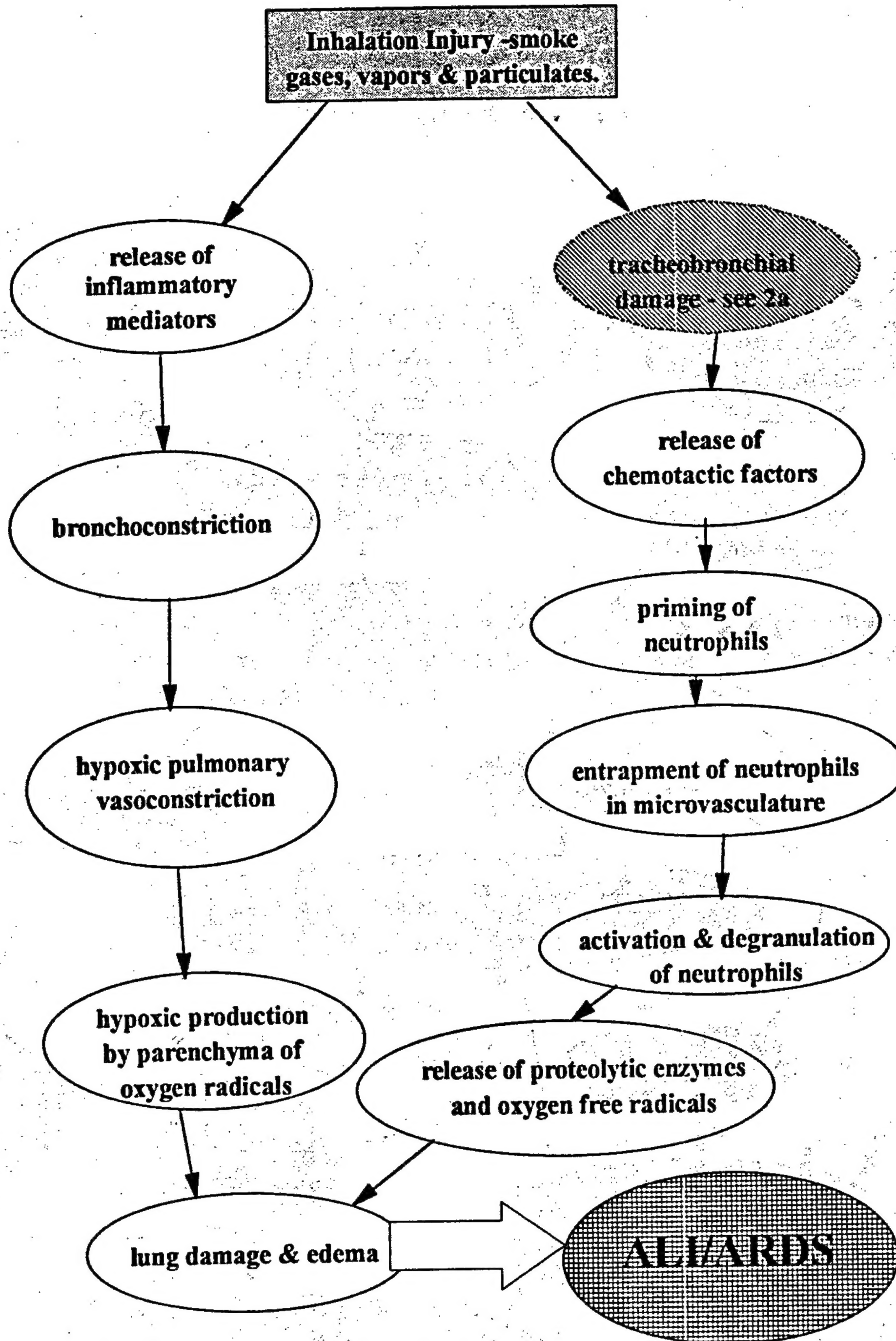

Fig. 2. pathogenesis of parenchymal damage by smoke

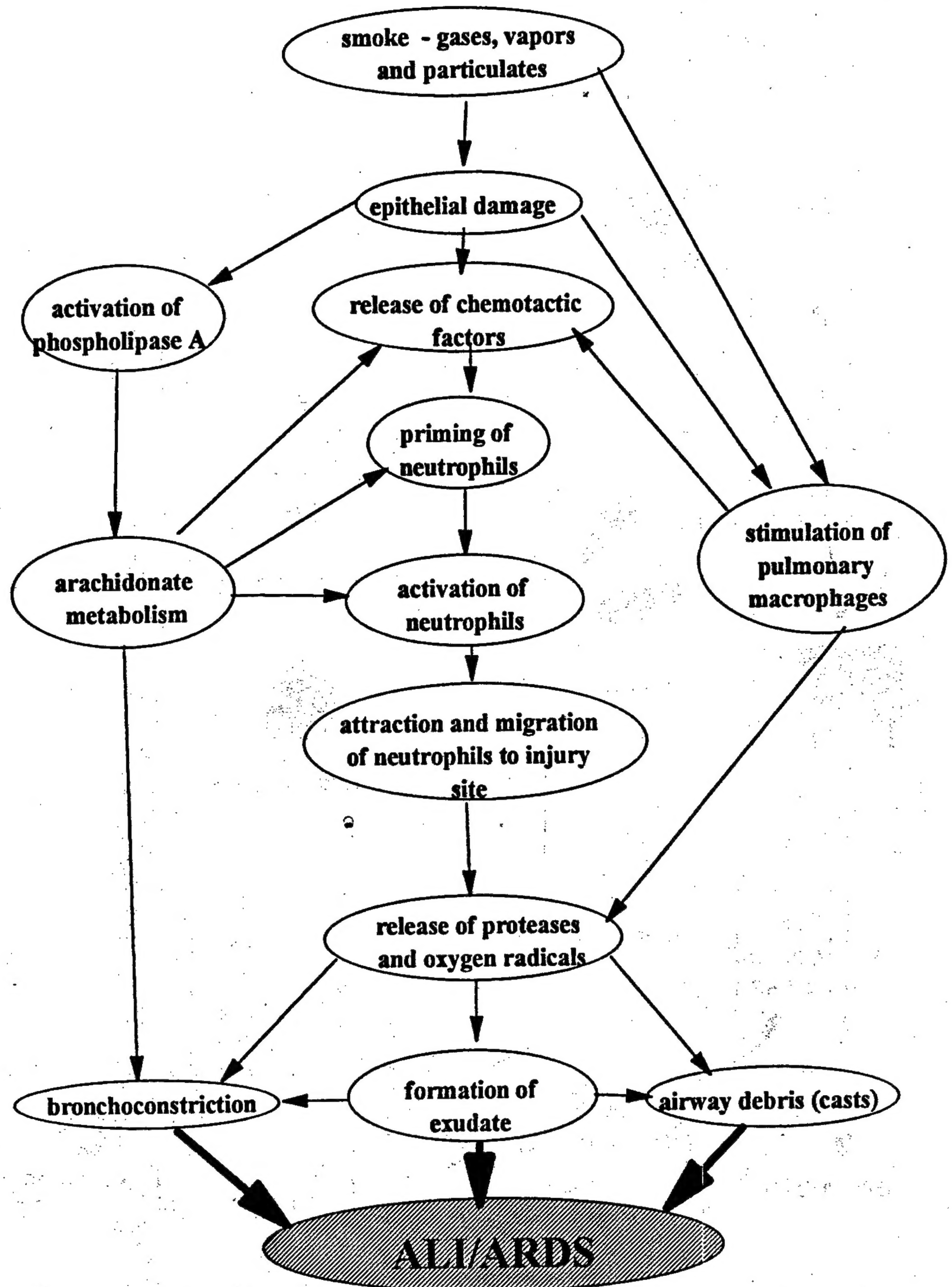

Fig. 2a. smoke induced tracheobronchial damage

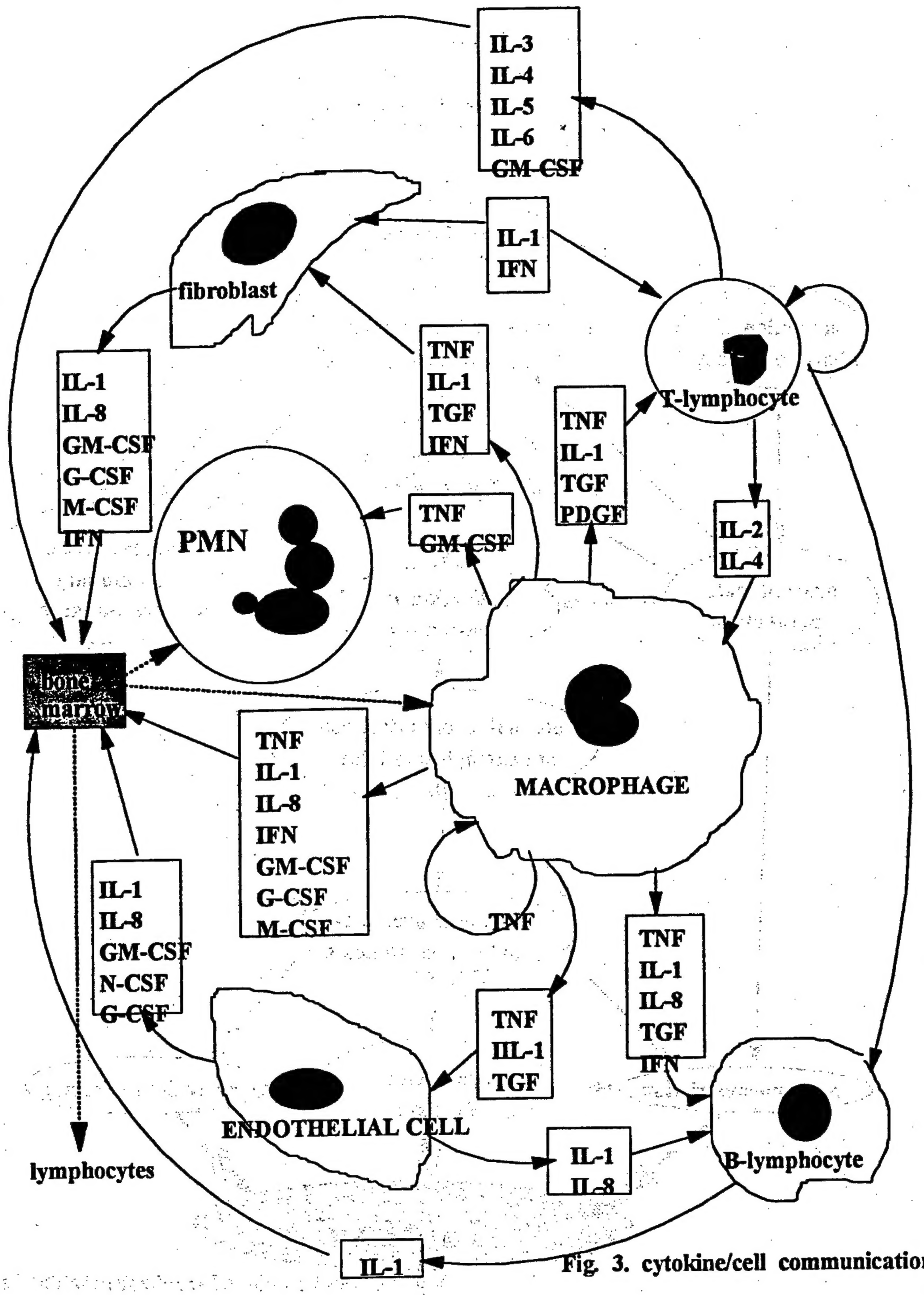

Fig. 3. cytokine/cell communication